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CARDIOVASCULAR SURGERY IN A CHILDREN'S HOSPITAL

I. ACYANOTIC LESIONS. A REVIEW OF 241 OPERATIONS

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AT THE Children's Hospital of Philadelphia, 434 cardiovascular operations were performed on 428 patients during the period from May, 1947, to July, 1958. In reviewing this experience, consideration will be given in this paper to the acyanotic group of patients and in a later paper patients in the cyanotic group will be reviewed.

PATENT DUCTUS ARTERIOSUS

The value of closure of a patent ductus arteriosus by ligation or division has been well established. Symptoms disappear and the heart returns to normal size following operation in early life.[1]

In the present series the operation has been performed successfully upon 160 children with a patent ductus and the characteristic continuous murmur below the left clavicle. The age range was from 4 months to 14 years, the greatest number being around the age of 4 years. Electrocardiograms were within normal limits for the age or showed a pattern indicative of the presence of left ventricular hypertrophy. These children were referred for operation without special studies. In all but 10 the ductus was obliterated by three individual ligatures of No. 0 silk. The thrill and continuous murmur due to the ductus disappeared in all patients following the operation. In no instance have we found recanalization of the ductus arteriosus.

Only when the patent ductus arteriosus was short and broad was it thought necessary to sever the vessel and suture the two ends as is recommended by many surgeons. This procedure was carried out in 10 children.

In individuals with a patent ductus and a continuous murmur the pressure in the aorta is greater than in the pulmonary artery both in systole and diastole. The shunt of arterial blood into the lungs may be large and pulmonary hypertension may exist in

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The anesthesia was administered by Dr. Margery Van N. Deming and her staff prior to September, 1955, and subsequently was administered by Dr. Leonard Bachman and his staff.

some individuals due to the increased flow. If pathologic changes develop within the intrapulmonary arterioles, however, they would seem to be reversible since all abnormal cardiac findings disappear in patients with a continuous murmur following closure of the patent ductus.

The situation is different in patients with a patent ductus who have only a systolic murmur or no murmur. All of these individuals have pulmonary hypertension. In those in whom a high level of resistance has developed within the lungs, the patent ductus may serve as an essential safety valve to the hypertensive right heart. The diagnosis can be made only with the aid of special diagnostic methods. Of 10 such children in our series the presence of a patent ductus was established by an arteriogram in 4 and by cardiac catheterization in 6. Three arteriograms were obtained from infants under 1 year of age; the fourth was from a 3-year-old child in severe congestive failure who weighed only 8 kilograms. The age of children in whom cardiac catheterization was performed ranged from 3 to 9 years.

In these 10 patients with pulmonary hypertension and a systolic murmur the ductus was large in all except one 5-year-old boy in whom a mild degree of coaretation of the aorta was also present. The diameter of his ductus was 0.5 cm. which was approximately the size of the ductus found in the 3 infants. The width of the ductus in the remaining 6 children varied from 1.2 to 2.0 cm. The ductus was ligated in 6 of these 10 patients and divided in 4. In 5 children in whom cardiac catheterization revealed balanced pressure in the aorta and pulmonary artery, an electromanometer was used at the time of operation to determine the effect of clamping the ductus on the pulmonary pressure. There was a definite drop of pressure in 2 patients and little or no change in 3. One child in whom the pressure fell was the boy with slight coaretation. However, no decrease in pulmonary pressure had occurred when cardiac catheterization was repeated one year later. In the second child, the ductus, which was 2.0 cm. wide and very short, was divided without difficulty but shortly after operation death occurred due to rupture of the pulmonary artery at a site proximal to the suture line (apparently at the position where a clamp had been applied). Death due to progressive pulmonary hypertension occurred 14 months after operation in a 9-year-old girl whose pulmonary pressure fell slightly during occlusion of the pulmonary artery. Whether the surgeon is warranted in closing a patent ductus in patients with pulmonary blood pressure equal to systemic pressure is a moot point at the present time.

Operations on Infants With Patent Ductus.—The first operation in infancy was performed January, 1949, on a 5-month-old girl in severe congestive failure who was unable to live out of oxygen during the 2 months preceding surgery. She was discharged a well baby 2 weeks after ligation of a patent ductus. Thirty operations have been performed on children under the age of 2 years, and 23 in the first year of life, the youngest being 4 months of age. Five infants 6 months of age or younger were in severe congestive failure with enormous hearts that filled the left chest making it difficult for the surgeon to obtain access to the vessels. In 3 the

left lung was atelectatic. Following the occlusion of the patent ductus, there was dramatic improvement together with immediate decrease in the size of the heart. In 4 additional infants unsuspected fluid was found in the pleural or pericardial cavity at the time of operation.

In earlier years operation in infancy was performed only in the presence of symptoms or undue cardiac enlargement. More recently, we have recommended operation at about 9 months in all babies with a continuous murmur unless the condition of the infant is such as to require earlier operation. However, we do not perform special diagnostic tests on the infant with a systolic murmur who is progressing favorably. After infancy, operation is deferred if possible until the age of approximately 4 years when the child can undergo the operative procedure without undue psychologic trauma.

There were 5 children operated upon in the hope that a patent ductus arteriosus might be found but in whom it was not present. In 4 a continuous murmur was heard. Two were in severe congestive failure at the time of operation. One, who has been reported previously,[2] died on the operating table. At necropsy, a ventricular septal defect and deformed aortic valve were found. Subsequently, it was discovered that a similar error in diagnosis had first been reported by Soulié.[3] The second child in failure, a 5-month-old infant with total transposition of the pulmonary veins, died one week postoperatively. A third child, on whom thoracotomy was performed in 1949, was thought to have a ruptured sinus of Valsalva preoperatively but was explored because of the possibility that the diagnosis might be incorrect. In the fourth child the ductus was present only as a ligamentous cord. Although the existence of a continuous murmur could be verified by direct auscultation over the pulmonary artery, no clue as to its origin could be found. The fifth child, an infant in whom an arteriovenous shunt at the level of the pulmonary artery had been detected by cardiac catheterization, proved to have no ductus open or closed. Presumably this boy has a truncus arteriosus from which the pulmonary artery arises.

ARTERIOVENOUS FISTULA

An arteriovenous fistula involving the left vertebral artery was resected in a 5-year-old boy in whom the site of the fistula had been verified preoperatively by angiocardiography.

VASCULAR RING CONSTRICTING TRACHEA AND ESOPHAGUS

The diagnosis of a vascular ring constricting the trachea and esophagus is not difficult provided the possibility is entertained. It is primarily a roentgenologic diagnosis and should be considered in any infant or child who has stridor and difficulty in swallowing.

Eleven patients with this diagnosis were seen and 12 operations were carried out upon them with 3 deaths resulting. The age range was from 8 days to 7 years. Eight children were below 8 months of age and 2 within the second year of life. A double aortic arch was present in 8 patients with a right descending aorta in 2. The remaining 3 patients had a right aortic arch and descending aorta and a left aortic diverticulum giving rise to a retroesophageal left subclavian artery and ligamentum arteriosum. Two

of the deaths occurred in newborn infants in whom the operation had been performed as an emergency procedure because of acute respiratory distress. In each instance the arch was severed successfully, but stridor and respiratory distress persisted until death on the second and eleventh postoperative day, respectively. A third child was subjected to a primary operation at the age of 12 months. She had a right aortic arch, right descending aorta, and a posteriorly situated left aortic diverticulum giving rise to a left subclavian artery and a ligamentum arteriosum. The left subclavian artery and the ligamentum arteriosum were severed and both vessels were dissected carefully back to their origin to free the vascular ring completely. The child, however, continued to have infections associated with stridor and respiratory distress. Roentgenograms showed a persistent extrinsic pressure defect in the esophagus at the level of the third thoracic vertebra with anterior displacement of the trachea. Seventeen months later she was readmitted for resection of the retroesophageal diverticulum. This was carried out successfully through a right thoracotomy. The child, however, developed a high fever, chills, and peripheral shock and died on the second postoperative day.

In all the operations to relieve the constriction of the vascular ring encircling the trachea and esophagus, the left chest was entered regardless of whether the aorta descended on the right or left side. A posterolateral incision was made at the fourth interspace. The advice of Gross[4] was carried out not only to divide the vessels but to displace them so as to remove all pressure upon the trachea or esophagus. In retrospect, it is uncertain whether the difficulty experienced in the 3 patients who died was brought about by the inadequate relief of pressure. In subsequent procedures, however, great care has been taken to relieve the pressure upon the trachea and esophagus completely. Even so, in some of our patients stridor has persisted to a lesser degree, particularly in times of infection. However, it has not been nearly the problem that it was preoperatively.

COARCTATION OF THE AORTA

Coarctation of the aorta of significant degree should be resected in childhood because of the relatively early death of a large proportion of individuals with this lesion and the increased hazard of hemorrhage as sclerosis and calcification develop in the wall of the aorta. Two 10-year-old boys with coarctation have died on the medical service at Children's Hospital of hemorrhage. One hemorrhage was cerebral; the other was from a saccular aneurysm which eroded through the esophagus.

Measurement of the blood pressure at rest gives little indication of the degree to which it may rise under stress. In the first 25 children of the present series, the systolic pressure in the arms at rest ranged from 100 to 160 mm. Hg and the diastolic pressure from 90 to 110 mm. Hg. In 5 children the maximum systolic pressure in response to a cold pressor test ranged from 180 to 198 and the maximum diastolic pressure from 120 to 140. The maximum systolic pressure at the time of operation ranged from 140 to 230 (average 190) and the diastolic pressure from 90 to 150 (average 115).

The usual site of coaretation is in the descending arch distal to the origin of the left subclavian artery. Since occasional cases have been reported in which the stricture was situated in the lower thoracic or abdominal aorta, it was our custom in preceding years to obtain an angiocardiogram in order to establish the site of coaretation. More recently, a study of overexposed conventional roentgenograms aided, if necessary, by spot films has supplied adequate confirmatory evidence in the majority of cases. When the coaretation lies in the descending arch, an indentation or concavity of the aorta to the right may often be visible above the level of the left pulmonary artery with abnormal convexity of the aorta distal to the indentation due to poststenotic dilatation (the 3 sign). There is corresponding deviation of the barium-filled esophagus to the right below the level of the aortic arch with indentation to the left (the ϵ sign)[6] (Fig. 1). Exaggerated pulsations of the cervical vessels often associated with a thrill provide additional evidence that the coaretation is situated in the arch of the aorta.

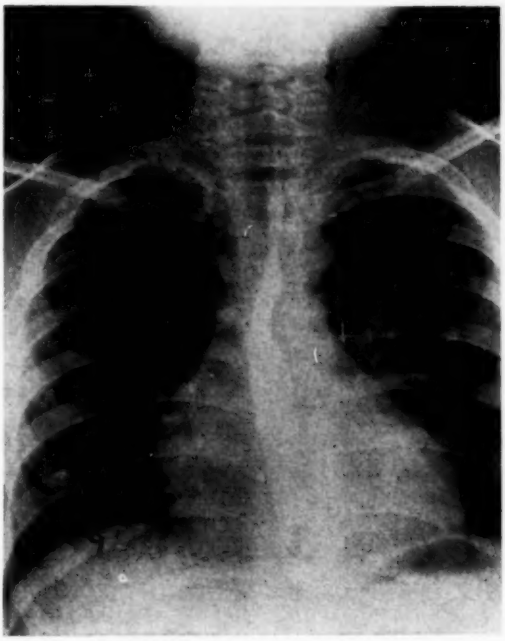

Fig. 1.—Roentgenographic signs in coarctation of the aorta. Note indentation of the aorta to the right above the level of the left pulmonary artery with convexity of the aorta distal to the indentation (3 sign) and corresponding deviation of the esophagus to the left at and below the level of the aortic arch (the ϵ sign).

Thirty-seven operations for coaretation of the aorta have been carried out, with one death 10 hours after operation due to a hemorrhagic transfusion reaction. This was brought about by the necessity of massive transfusions due to a technical error. The age range was 2 to 14 years. Twelve

of the patients were 9 years of age. A patent ductus was found in 13 children, a saccular aneurysm distal to the site of stenosis in 2, mitral stenosis in 4, and an anomalous subclavian artery in 3. One child with an anomalous subclavian artery also had dextrocardia with a right aortic arch, right descending aorta and absent inferior vena cava proved by angiocardiography.

In children the vessels are still elastic and pliable and the operative procedure can be carried out with a minimum of difficulty. Interrupted sutures were used in all patients since previous studies had indicated that growth of the aorta at the site of the anastomosis might be interfered with by a continuous suture.[5] In two children, the defect was long and it was necessary to use a plastic procedure in order to reconstruct an artery of normal size without the use of a graft.[6] In 7 children the defect was quite long and high and the anastomosis was made between the descending aorta and the inferior surface of the transverse aortic arch as it continued out into the subclavian artery, making essentially an end-to-side anastomosis. It is felt that in children some type of anastomosis can always be accomplished without utilizing a graft which probably will not increase adequately in size during growth.

Hypothermia was used in 2 children in whom there seemed to be a minimum of collateral circulation. In addition, hypothermia was used in one 2-year-old girl in congestive failure who had coaretation of the aorta with mitral stenosis, a patent ductus arteriosus, and pulmonary hypertension. In this child, the ductus was as large as the pulmonary artery. The systolic pressure in the pulmonary artery at the time of operation was 120 mm. Hg. It was thought that this did not change at the completion of the operation. However, when the child returned for cardiac catheterization one year later, the pulmonary artery pressure had returned to normal.

Two children in whom the operation was performed at 2 and 3 years, respectively, because of persistent undue hypertension had suffered severe congestive failure in early infancy from which they recovered under medical treatment. In a larger group of children with a similar history of congestive failure in infancy but in whom the blood pressure has dropped to a relatively low level following recovery, operation is being postponed until about the age of 9 years.

The incidence of psychoneurotic and abdominal complications in the postoperative period has been high. Ten children manifested emotional disturbances. Nine developed abdominal symptoms with ileus in 2. Necrotizing arteriolitis of the abdominal vessels with gangrene of the bowel has been reported following resection of coaretion. When abdominal symptoms are associated with an exacerbation of hypertension postoperatively, it has been suggested that the early use of hypotensive agents such as hydralazine and reserpine may result in subsidence.[8]

Decortication of the lung was required in one child one month after removal of a coarcted segment of the aorta.

ATRIAL SEPTAL DEFECT

Children with atrial septal defect are now operated on as a matter of

election if they present roentgenographic and electrocardiographic evidence of enlargement of the right atrium and right ventricle together with pulmonary flow at least twice the systemic flow as indicated by cardiac catheterization. These children usually have an overactive cardiac impulse, a widely reduplicated second pulmonary sound, either no thrill or a faint systolic thrill immediately to the left of the sternum in the second and third left interspaces, and a low-pitched systolic murmur maximum in the pulmonary area and often heard over the entire chest. In quality, this murmur resembles the innocent murmur heard not uncommonly in the pulmonary region. A third heart sound or mid-diastolic blow is often audible to the left of the lower sternum.

The operation is performed through a right thoracotomy in the fourth interspace with the aid of hypothermia and direct vision, using inflow occlusion.[9] The temperature is lowered to about 31° C. We feel that this is a safe procedure as long as the period of total inflow occlusion does not exceed 4 or 5 minutes. If the closure of the atrial septal defect cannot be completed within this period of time, the atrium is closed and normal circulation allowed for at least ten minutes before utilizing a second period of direct vision. Continuous electrocardiographic monitoring is maintained. There is usually a period of cardiac arrhythmia after the clamps are removed from the vessels and circulation is resumed. Care is taken not to disturb the heart during this period until the rhythm is restored to normal. The blood loss at the time of operation and postoperatively is replaced as accurately as possible but otherwise fluids are restricted. It has been our custom to heparinize these patients starting at the end of about 48 to 72 hours in the hope of avoiding emboli from the line of suture.

It is well not to select children for closure of an atrial septal defect under hypothermia who show prolongation of the P-R interval in the electrocardiogram since it is conceivable that they may have a defect in the lower portion of the septum above the atrioventricular valves (ostium primum). We have also deferred operation on children with the characteristic electrocardiogram and apical systolic blow due to a common atrioventricular canal.[10] Surgical correction of an ostium primum or common atrioventricular canal can be performed only with the aid of extracorporeal circulation.

A septal defect situated at the site of the foramen secundum has been closed successfully in 8 children ranging in age from 5 to 13 years. The defects were large in 4, medium-sized in 3, and small in one. Circulatory occlusion was maintained for periods ranging from 2½ to 5 minutes.

PARTIAL TRANSPOSITION OF PULMONARY VEINS

In 6 additional patients, there was anomalous drainage of one or more right pulmonary veins in addition to the atrial septal defect (Fig. 2). In 5 patients, aged 6 to 8 years, the anterior edge of the septal defect was attached anterior and to the right of the anomalous veins, thus closing the defect and transposing the opening of the anomalous right-sided pulmonary veins into

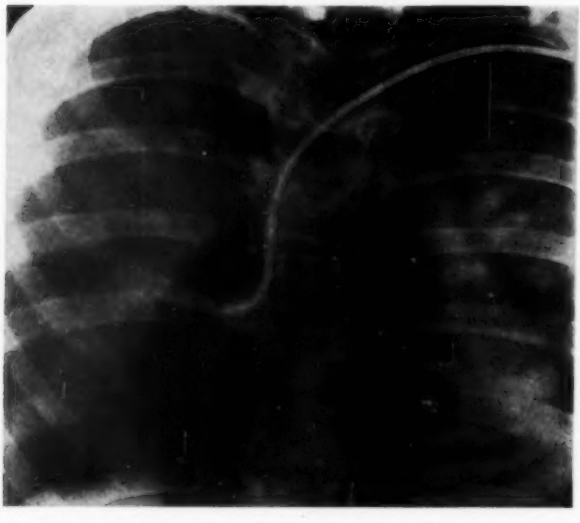

Fig. 2.—Anomalous drainage of right pulmonary vein. Note passage of catheter from superior vena cava into a pulmonary vein within the lungs. The diagnosis was proved by operation.

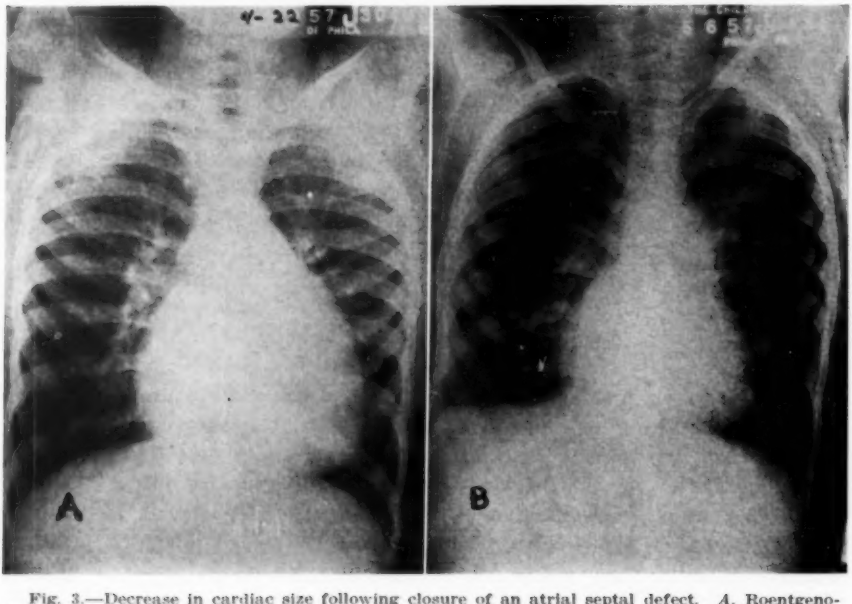

Fig. 3.—Decrease in cardiac size following closure of an atrial septal defect. *A*, Roentgenogram taken on day preceding operation. *B*, Two weeks after closure of atrial defect. From a 10-year-old girl.

the left atrium. In 2 children it was necessary to use two periods of circulatory occlusion to complete the procedure. In one child a small defect, 1 cm. in diameter, which might not have been revealed except under direct vision, was closed together with a large defect, 4 by 5 cm. in size. In two children the right pulmonary veins entered the superior vena cava about 2 cm. above the heart. It was possible to use a purse-string type suture which caused the pulmonary veins to enter the left atrium and the superior vena cava to enter the right atrium.[9] In the sixth case the pulmonary veins opened into the superior vena cava 4 cm. from the heart. The technical difficulties anticipated in correcting this deformity were magnified by severe cardiac arrhythmias even without circulatory occlusion. The operation was abandoned perhaps unwisely.

The postoperative course has been relatively uneventful in the 13 patients in whom a definitive procedure was performed. Disappearance of the murmur previously noted and decrease in heart size (Fig. 3) has occurred in all cases together with rapid growth and weight gain.

CONSTRICTIVE PERICARDITIS

Two children were operated upon for constrictive pericarditis. A transsternal incision was used in each instance and the pericardium was removed from the phrenic nerve on the one side to the phrenic nerve on the other. Excellent results were obtained in both cases.

There were 241 operations on 239 acyanotic individuals with 6 deaths (2.5 per cent). We have excluded from this group 2 children with lesions associated with cyanosis who were explored for the possible presence of a patent ductus, and have included a 13-year-old boy with valvular pulmonary stenosis and intact ventricular septum who was dyspneic but not cyanotic when valvotomy was performed (Table I).

TABLE I. OPERATIONS ON ACYANOTIC LESIONS

	NUMBER OF OPERATIONS PERFORMED	DEATHS	
		NUMBER	PER CENT
Patent ductus arteriosus	170	1	0.6
Vertebral A.V.* fistula	1	0	—
Coaretation of aorta	37	1	2.7
Double aortic arch	12	3	25.0
Atrial septal defect	8	0	—
Partial transposition of pulmonary veins	5	0	—
Valvular pulmonary stenosis	1	0	—
Constrictive pericarditis	2	0	—
Decortication of lung	1	0	—
Exploratory	4	1	25.0
Total	241	6	2.5

*A.V. = Arteriovenous.

SUMMARY

1. Four hundred and thirty-four cardiovascular operations were performed at Children's Hospital between May, 1947, and July, 1958. The 241 operations carried out on acyanotic children have been reviewed.

2. One hundred and sixty patients with patent ductus arteriosus who had a continuous murmur were operated

upon, with no deaths. Ligation with three silk ligatures was used in 150 of these children. There have been no cases of recanalization of the patent ductus arteriosus. In 10 instances of patent ductus arteriosus with pulmonary hypertension, the diagnosis was made by special studies in the absence of a continuous murmur. There was one death due to operation and a subsequent death due to persistence of pulmonary hypertension.

3. Twelve patients with vascular rings constricting the trachea and esophagus were operated upon, with 3 deaths, 2 of which were in newborn infants.

4. Thirty-seven operations were carried out for coarctation of the aorta, with one death. We believe it is important to operate upon individuals with coarctation during childhood when the arteries are pliable and an anastomosis can almost invariably be performed without the use of grafts.

5. Thirteen patients with atrial septal defects were operated upon and 5 of these included anomalous venous drainage of right pulmonary veins. The operation was carried out under direct vision, using hypothermia and inflow occlusion, intermittent when necessary. There were no deaths and the results have been very gratifying.

6. Two boys with constrictive pericarditis were operated upon, with good results.

7. An arteriovenous fistula involving the left vertebral artery was resected in a 5-year-old boy.

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PLETHORA IN THE NEWBORN INFANT ASSOCIATED WITH CYANOSIS AND CONVULSIONS

A Review of Postnatal Erythropoiesis

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HIGH erythrocyte values are accepted as being normal in the neonatal period. An abnormal degree of plethora associated with anorexia, lethargy, cyanosis, and major convulsions has not previously been considered in the pediatric literature. Two infants seen in the Evanston Hospital newborn nursery presented these findings. Clinical improvement was observed after they were bled and given plasma transfusions. These cases are reported, and a brief discussion of the possible mechanisms is given.

Blood count, hemoglobin, and hematocrit determinations were done on capillary samples. Hemoglobin values were determined by the cyanmethemoglobin technique described by Drobkin[1] and were read on a Leitz Photrometer. An International Microhematocrit Centrifuge was used in determining microhematocrit values. Photoelectric examination of hemoglobin was done on a Coleman Junior Photoelectrometer. Fetal hemoglobin concentration was determined by means of the alkali denaturation technique described by Singer and associates.[2]

CASE REPORTS

Case 1.—M. T. was born on March 31, 1956, after a normal pregnancy, labor, and delivery. The first day of the mother's last menstrual period was June 20, 1955; the expected date of delivery was April 7, 1956. The infant weighed 6 pounds, 3 ounces at birth, was 19 inches in length, and appeared normal. The mother was a healthy 44-year-old gravida vii, para v. She was Rh negative and the father Rh positive, but there was no history of erythroblastosis in the five siblings, who were in good health. There had been one spontaneous abortion. Both parents were of Scottish descent.

The infant was first examined at the age of 9 hours. The child was active and unusually alert. There were no abnormal physical findings except moderate dryness and peeling of the skin. The blood type was CDe; the Coombs' test was negative. The blood count findings were: hemoglobin, 31 Gm. per 100 ml.; red blood cells, 6,890,000 per cubic milliliter; white blood cells, 13,600 per cubic milliliter. In the differential count there were 71 per cent neutrophils, 20 per cent lymphocytes, and 17 per cent eosinophils. There were 8 erythroblasts per 100 white blood cells.

Feedings were started at the age of 16 hours and were accepted with normal interest. At 36 hours of age the infant suddenly developed episodes of apnea and cyanosis, each lasting 1 to 3 minutes and occurring at about 30-minute intervals. They were not related to feedings or associated with regurgitation. There was no evidence of respiratory distress. Twitching of the eyelids was observed during some of these episodes. One, occurring approximately 8 hours after the onset, terminated in a generalized clonic convulsion.

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On physical examination the infant was well hydrated, well nourished, and did not appear ill. During the episodes of apnea, the infant was deeply cyanotic. Between attacks, the skin was magenta in color. No abnormality of the eyes, nose, or throat was found. The apex beat was in the fourth left intercostal space in the nipple line; the rhythm was sinus; and there was no murmur or thrill. The lung fields were clear. The abdomen was soft, and no organs or masses were palpable except the liver edge, which could be felt at the right costal margin. The deep reflexes were active and equal bilaterally; no abnormal reflexes were elicited. The fontanel was full but not bulging.

was normal. Subdural and ventricular punctures were done and demonstrated no evidence of subdural fluid or abnormality of the ventricles. The cerebrospinal fluid was clear.

The infant was placed in an Isolette in oxygen. Procaine penicillin was given intramuscularly daily. Oral feedings were stopped, and 5 per cent glucose in water was given subcutaneously. At 90 hours of age, 30 c.c. of whole venous blood was removed, and 30 c.c. of plasma was given intravenously.

Twelve hours later, the hemoglobin was 28.8 Gm. per 100 ml.; the red blood cell count was 6,810,000 per cubic milliliter; and the hematocrit was 69 per cent. The platelet count

TABLE I. HEMATOLOGIC DATA ON CASE I (M. T.)

DATE	AGE (DAYS)	WEIGHT	RED BLOOD CELLS (MILLIONS/ MM.^{3})	HEMATOCRIT (ML./ 100 ML.)	MCV (μ^3)	HEMOGLOBIN (GM./ 100 ML. BLOOD)	MCH $\gamma\gamma$G	MCHC (GM./ 100 ML. ERYTHROCYTES)	PLATELETS (THOUSANDS /MM.^{3})
3/31/56	0	6 lb. 3 oz.	6.89			31.0	45.0		
4/2/56	2		6.56	83	126.5	29.6	42.3	35.7	
4/3/56	3		6.81	69	101.5	28.8	41.1	41.8	98
4/4/56	4		5.67	71	125.0	26.4	46.5	37.2	87
4/6/56	6	5 lb. 12 oz.	5.62	66	119.0	24.2	43.0	36.7	168
4/9/56	9	6 lb. 3½ oz.	5.98	67	112.0	23.4	39.1	35.0	174
4/11/56	11	6 lb. 5¾ oz.		58.5		20.0			194
4/14/56	14		5.32	59	110.0	21.4	40.2	36.3	
7/3/56	94		3.96	34.5	87.2	11.5	29.0	33.4	312
1/10/57	285		4.54			13.1	28.9		

Laboratory examinations were done (Table I). The blood count findings were: hemoglobin, 29.6 Gm. per 100 ml.; red blood cells, 6,560,000 per cubic milliliter; hematocrit, 83 per cent; white blood cells, 7,700 per cubic milliliter. The differential count showed 80 per cent neutrophils and 20 per cent lymphocytes. No abnormal hemoglobin was found on electrophoretic examination. Determination of the fetal-adult hemoglobin ratio was not done. A blood culture produced no growth on aerobic or anaerobic media. The Coombs' test was repeated, and again was negative. The findings on x-ray examination of the chest were normal. A patent upper airway was visualized by direct laryngoscopy. An electrocardiogram

was 98,000 per cubic milliliter. The bleeding time was 1 minute, 15 seconds, and the capillary clotting time was 2 seconds. The reticulocyte count was 2.6 per cent. At 14 days of age the hemoglobin was 21.4 Gm. per 100 ml.; the red blood cell count was 5,320,000 per cubic milliliter; and the hematocrit was 59 per cent. The white blood count was 9,000 per cubic milliliter; and the differential white blood count showed 55 per cent neutrophils, 28 per cent lymphocytes, 14 per cent neutrocytes, and 3 per cent eosinophils. The platelet count was 194,000 per cubic milliliter.

Following the venesection and plasma transfusion, the episodes of apnea and cyanosis ceased although the skin color remained purplish-red.

During the next 24 hours, moderate jaundice developed which gradually subsided over a 4-day period. The subsequent course was that of a normal infant. Oxygen was discontinued, and feedings were resumed. He was discharged from the nursery on April 13, at 14 days of age, clinically well.

CASE 2.—J. A.* was born on Dec. 2, 1957, after a normal pregnancy, labor, and delivery. He was the first child of a healthy 36-year-old gravida i. The first day of the last menstrual period was Jan. 29, 1957; the expected date of delivery was Nov. 5, 1957. The parents were Swedish.

At the time of delivery, the vernix caseosa was stained deep yellow. The infant presented no abnormal physical findings except cyanosis of the hands and feet. In the absence of other abnormal signs, this was interpreted as being within normal limits. He weighed 7 pounds, 4½ ounces and was 20 inches long. The mother was Rh negative and the father was Rh positive. There was no Rh antibody titer during pregnancy.

Laboratory studies were done (Table II). The infant was Rh negative (cde). The hemoglobin was 31.4 Gm. per 100 ml.; and the red blood cell count was 7,740,000 per cubic milliliter. The white blood cell count was 24,050 per cubic milliliter. The differential count showed 76 per cent neutrophils, 17 per cent lymphocytes, 2 per cent monocytes, 3 per cent eosinophils, 1 per cent metamyelocytes, and 1 per cent myelocytes. There were 3 erythroblasts per 100 white blood cells.

The infant appeared to be healthy for the first two days. Feedings were started at 18 hours and were accepted fairly well. On the third day he became lethargic and refused feedings. Within the next 12-hour period, apnea and generalized cyanosis developed in association with clonic convulsions. Feedings were stopped, and the infant was placed in an Isolette in oxygen. Dicrysticin was given intramuscularly, and phenobarbital was given hypodermically.

A blood count showed the following: hemoglobin, 31.5 Gm. per 100 ml.; red blood cells, 8,060,000 per cubic milliliter; and venous hematocrit, 73 per cent. Four hours after the initial convulsion, a venepuncture was done. Forty cubic centimeters of blood was removed, and 55 c.c. of plasma was given intravenously. Within 12 hours the infant's condition seemed improved; however, he continued to be lethargic and had occasional twitching of the face, hands, and extremities. A second venepuncture was done 48 hours after the first. Thirty cubic centimeters of blood was removed and 40 c.c. of plasma infused.

Oral feedings were resumed on the fifth day of life. They were accepted fairly well but were associated with a moderate amount of regurgitation. By

TABLE II. HEMATOLOGIC DATA ON CASE 2 (J. A.)

DATE	AGE (DAYS)	WEIGHT	RED BLOOD CELLS (MILLIONS/ MM.³)	HEMATOCRIT (ML./ 100 ML.)	MCV (μ³)	HEMOGLOBIN (GM./ 100 ML. BLOOD)	MCH γγG	MCHC (GM./ 100 ML. ERYTHROCYTES)	PLATELETS (THOUSANDS /MM.³)
12/2/57	0	7 lb. 4½ oz.	7.74			31.4	40.6		
12/5/57	3	6 lb. 11 oz.	8.06	73	90.6	31.5	38.9	42.5	
12/6/57	4		7.85	68	81.6	24.8	31.6	35.3	60
12/7/57	5		7.90	74	93.6	23.6	29.9	31.9	
12/9/57	7		6.25	70	112.0	27.4	43.7	39.2	
12/10/57	8	7 lb. 1½ oz.	5.88	65	110.6	25.0	41.8	38.4	133
12/13/57	11	7 lb. 3 oz.	5.76	72	125.0	22.6	29.1	31.4	
12/16/57	14	7 lb. 6½ oz.	5.80	60	103.4	20.0	34.6	33.2	
12/26/57	24		4.69	44		15.3	32.6		
9/27/58	299		4.65	39	83.9	14.25	30.6	36.6	

*A patient of Dr. John M. Reichert.

TABLE III. BLOOD ERYTHROCYTE, HEMOGLOBIN, AND THROMBOCYTE VALUES

AGE	ERYTHROCYTE COUNT (MILLIONS/MM.^{3})		RETICULOCYTE COUNT (PER CENT TOTAL ERYTHROCYTES)		ERYTHROCYTE PACKED VOLUME (ML./100 ML. BLOOD)	ERYTHROCYTE VOLUME (μ^3)	HEMOGLOBIN CONCENTRATION (G/100 ML. BLOOD)		ERYTHROCYTE HEMOGLOBIN CONTENT ($\gamma\gamma$G)	ERYTHROCYTE HEMOGLOBIN CONCENTRATION (GM./100 ML. ERYTHROCYTES)	THROMBOCYTE COUNT (THOUSANDS/MM.^{3})	
	VALUE	RANGE	VALUE	RANGE	VALUE	VALUE	VALUE	RANGE	VALUE	VALUE	VALUE	RANGE
Birth	5.7	4.8-7.1	4.35	2.50-6.50	56.6	106	21.5	18.0-27.0	38.0	38.0	227	140-290
One week	5.3	4.5-6.4	1.12	0.10-4.50	52.7	101	19.6	16.2-25.5	37.0	37.2	235	150-320
Twelve months	4.6	4.0-5.5	0.90	0.60-1.70	35.2	77	11.6	9.0-14.6	25.0	33.0	345	218-470
Six years	4.7	3.8-5.4			37.9	80	12.7	10.0-15.5	27.0	33.5		
Twelve years	4.8	3.8-5.4			39.6	81	13.4	11.0-16.5	28.0	33.8		
Average adult	5.1	4.2-6.2	1.5	0.5 -3.8	44.5	87	14.9		29.0	33.5	409	273-545

Data from E. C. Albritton: *Standard Values in Blood*, p. 46, table 46.[3]

the sixth day of life, there was definite improvement in the infant's condition. The color was less dusky, and he was alert and active. Medications were discontinued. He was discharged from the hospital clinically well at 15 days of age.

Twelve hours after the first venepuncture, the hemoglobin was 24.8 Gm. per 100 ml.; the red blood count was 7,850,000 per cubic milliliter; and the hematocrit was 68 per cent. The platelet count was 60,000 per cubic milliliter. On the seventh day of life, the hemoglobin was 27.4 Gm. per 100 ml.; the red blood count was 6,250,000 per cubic milliliter; and the hematocrit was 70 per cent. In the following week the red blood count fluctuated between 7,450,000 and 5,020,000 per cubic milliliter; and the hematocrit dropped to 60 per cent. On the eighth day of life, the platelet count was 133,000 per cubic milliliter. The reticulocyte count was 0.1 per cent. The bleeding time was 40 seconds, and the capillary clotting time was 4 minutes. An electrophoretic study of the hemoglobin showed 26.6 per cent fetal and 63.4 per cent adult hemoglobin.

DISCUSSION

Erythrocyte values in the neonatal period are high and show a wide range of normal (Table III). The source of sampling is one factor which must be taken into consideration when interpreting blood counts in the newborn infant. This has been emphasized by Smith,[4] who compared the findings of several workers in correlation with the source of sampling. Erythrocyte values of capillary blood are significantly higher than those of venous blood. The average red blood count is 804,000 per cubic milliliter and the hemoglobin 2.85 Gm. per 100 ml. higher in the capillary samples. The venous hemoglobin is, in turn, approximately 2 Gm. per 100 ml. higher than that of cord blood. The time of sampling is also of importance. In the premature and full-term infant, erythrocyte values increase for the first 2 to 24 hours after birth.

A heterogeneous red blood cell population contributes to the variability, and the predominance of macrocytic cells contributes to the high hemoglobin and hematocrit values. When compared with other age groups, the red blood cell count and mean corpuscular hemoglobin concentration are not much above those of the adult. However, the mean corpuscular volume, hemoglobin concentration, and mean corpuscular hemoglobin are significantly higher. Normoblasts may normally be as high as 10 per 100 white blood cells at birth. The reticulocyte count is from 2.50 to 6.50 per cent total erythrocytes. Active erythropoietic tissue is thought to be responsible for these findings. This apparently ceases rather abruptly after birth; at the end of the first week, normoblasts are not normally present, and the reticulocyte count has decreased from 0.1 to 4.5 per cent total erythrocytes.

Erythrocyte values may be affected by the time of clamping of the cord. The effect of early and delayed clamping of the cord on the erythrocyte values has been carefully studied by DeMarsh and co-workers.[5] They found significantly higher erythrocyte values on the third day of life in infants whose cords were clamped after placental separation than those in whom the cord was clamped immediately after the second stage of labor. These findings have recently been challenged by Whipple, Sisson, and Lund.[6] Their study included 28 infants who were the products of uncomplicated deliveries in healthy mothers. The time of clamping of the cord resulted in no significant difference in erythrocyte

values in the infants. It was only when the cord was vigorously stripped that an increase was seen. Sisson and Lund[7] also studied a group of 36 infants of anemic and nonanemic mothers in whom no difference was shown in blood counts due to the effect of placental transfusion.

Abnormalities of erythrocyte values due to structural defects in the placenta are well documented. Anemia in the newborn infant secondary to hemorrhage of the fetus into the mother's circulation was first established by Chown.[8] Although not common, several additional cases have been reported (Gunson,[9] Shiller,[10] and McGovern and associates[11]). Mixed blood groups in binovular twins were reported by Nicholas and co-workers,[12] and by Booth and associates.[13] A communication between the placentae was postulated permitting an exchange of erythroblasts and producing permanently mixed blood types. Klingberg and co-workers[14] reported a case of uniovular twins in which one was anemic and the other plethoric. The placenta was examined, and a parabiotic circulatory system was demonstrated by perfusion. No case is known in which plethora in the newborn infant has resulted from hemorrhage of maternal blood into the fetal circulation.

The significance of prenatal hypoxia with respect to erythrocyte values is not clear. Walker and Turnbull[15] studied fetuses and infants from 145 normal pregnancies and from 123 cases associated with fetal distress. They showed an increase in hemoglobin and red blood cell count associated with low oxygen content and saturation in blood samples from the umbilical vessels. Their conclusions were that an increase in hemoglobin and red blood cells occurs in the fetus as a part of normal growth. Any factor which will interfere with oxygenation of the fetus for a prolonged period of time will stimulate erythropoiesis and produce a further secondary increase.

Failure to differentiate the findings in postmature infants from those in infants who have sustained intrauterine hypoxia has contributed to the variation in results found by other investigators. Sjostedt and associates[16] reviewed this controversy and reported a study of 1,171 newborn infants. Evidence of impaired oxygen supply was found in 16.7 per cent of the cases in their group. Decreased oxygen saturation in the cord blood was correlated with an increase in hemoglobin. They stated that although the increased hemoglobin concentration suggests hypoxia, it may represent hemoconcentration. In a study of 152 newborn infants, Cook and co-workers[17] found a significant increase in hemoglobin in 28 infants who had experienced intrauterine hypoxia. On the basis of clinical findings and the lack of reticulocyte response, they postulated that these changes were the result of hemoconcentration rather than an acceleration of erythropoiesis.

The relationship of hypoxia to macrocytosis, hemoglobin concentration, and the percentage of fetal hemoglobin is not clear. After the thirty-sixth week of pregnancy, Walker and Turnbull[18] demonstrated a marked increase in the percentage of adult hemoglobin associated with the appearance of smaller, more mature erythrocytes. In the fetus that was subjected to prolonged hypoxia, erythrocyte values increased, the increase being due to the production of macrocytic

cells. There was also an increase in the amount of fetal hemoglobin.

The increase in fetal hemoglobin has not been substantiated by other workers. Cook and associates[17] show an inverse relationship between gestational age and the percentage of fetal hemoglobin. A decrease of 2.5 to 4.0 per cent fetal hemoglobin per week after the thirty-fourth week is correlated with gestational age and not with the time of birth or with changes in oxygen saturation of the umbilical vessels. Abrahamov and co-workers[19] found a steady decrease in the concentration of fetal hemoglobin in the fetus after 36 weeks' gestation. They postulated that since adult blood has less affinity for oxygen than fetal blood, a high concentration of adult hemoglobin in the postmature infant may actually contribute to anoxia.

High erythrocyte values indicate a disproportion between red blood cell mass and plasma volume irrespective of the total blood volume. High values might indicate an actual increase in red blood cell mass, or there could be a relative increase because of a low plasma volume. The total blood volume may be high with a relatively greater increase in red blood cell mass than in plasma volume. Mollison and co-workers[20] determined the red blood cell mass and plasma volume independently in 38 newborn infants. They showed an inverse linear relationship between the red blood cell mass and plasma volume when the hematocrit was between 37 and 55 per cent. With hematocrits over 55 per cent, however, there was a disproportionate increase in red blood cell mass and evidence of an increased total blood volume.

The significance of thrombocytopenia in the presence of plethora is not known. If an actual increase in total blood volume is present, a low platelet count might be the result of dilution. Thrombocytopenia is sometimes found in association with the polycythemia of cyanotic congenital heart disease. Adams and Cunningham[21] determined the platelet counts in 16 children with cyanotic congenital heart disease. They found values ranging from 60,000 to 200,000 per cubic milliliter. Examination of the bone marrow in these cases showed no significant abnormality with respect to platelet production.

Clinically, interference of the blood supply to the fetus is manifest in the newborn infant as the placental dysfunction syndrome. The entity has been described in detail and classified by Clifford.[22] The diagnosis is suggested before delivery by evidence of uterine shrinkage, maternal weight loss, and signs of fetal distress. Meconium-stained amniotic fluid and oligohydramnios may be observed at the time of delivery. There are physical signs of malnutrition in the infant and, frequently, there is evidence of recent weight loss. The appearance is that of an older infant; wakefulness is usually striking. There may be meconium staining of the skin, nails, and vernix caseosa. In the postmature infant, there is a paucity of vernix, and the skin is dry and parchmentlike.

In the two cases reported here the common causes of apnea, cyanosis, and convulsions in the newborn infant were initially considered. There was no indication of dehydration due to fluid loss. Weight loss was not excessive, the urinary output was normal, and neither infant was febrile. Neither infant appeared toxic or demonstrated evidence of infection.

Physical findings were not suggestive of cyanotic congenital heart disease. In each case the heart was not abnormal in size, and no murmur was audible. Normal heart size was shown on roentgen examination in Case 1 (M. T.), and the electrocardiogram was normal.

Pulmonary ventilation was adequate; respirations were quiet between the episodes of apnea. Laryngoscopic examination and roentgen examination of the chest in Case 1 showed normal findings.

The episodes of apnea were suggestive of an abnormality of the central nervous system. In Case 1 there was no other evidence of neurologic abnormality. Findings on subdural and ventricular punctures were normal. Primary central nervous system pathology was discounted in Case 2 (J. A.) because of the absence of other abnormal neurologic signs, and on the basis of the similarity of this to the previous case.

Blood chemistry examinations were not done in either case. There was no clinical evidence to support the possibility of a metabolic disturbance. The ruddy cyanosis shown by these infants was striking and unusual and was in keeping with the hematologic findings.

Both mothers were healthy and had normal blood counts at the time of delivery. The fact that both were Rh negative seems coincidental. In Case 1 there were no signs of erythroblastosis, and the Coombs' test was negative on two examinations. The blood type in Case 2 was Rh negative. The labors and deliveries were uneventful in both, and there was no unusual manipulation of the cord in either case.

Evidence of the placental dysfunction syndrome was present in these infants. The clinical syndrome presented may be a manifestation of the placental dysfunction syndrome. Evidence was only suggestive in Case 1. The mother was 44 years of age, but there was nothing unusual about this pregnancy in comparison with her five other successful pregnancies. The infant was born at the expected time, and the placenta appeared normal grossly. The infant was small, unusually wakeful, and had marked dryness and peeling of the skin. A definite diagnosis of the placental dysfunction syndrome could be made in Case 2. The mother was a 36-year-old primipara, and the gestation period was 44 weeks. Nothing abnormal was reported in the gross examination of the placenta; however, the vernix caseosa was stained yellow. The infant was small, unusually wakeful, and his skin was dry and peeling.

Erythrocyte values were abnormally high at birth in both cases, and there was no significant postnatal increase. The onset of clinical signs was not associated with detectable evidence of hemoconcentration or with an increase in erythrocyte values. There was no clinical evidence of dehydration.

The mechanism of the production of convulsions is not known. The red blood cell mass and plasma volume were not known in either case. On the basis of the findings of Mollison and associates,[20] an increased total blood volume with a disproportionate increase in red blood cell mass would have been present at birth. During the early postnatal starvation period, there was only a minimal weight loss in each. Nadal and co-workers[23] demonstrated an equal loss of water from all body tissues when dehydration was due to water deprivation alone. This

implies a decrease in total blood volume toward normal with the persistence of a relative increase in red blood cell mass. Sludging of the blood and capillary stasis might result in cerebral anoxia.

The symptomatology in these infants presented a serious clinical problem. The treatment seemed conservative in view of the clinical findings and the limited information as to the hematologic status. Replacing an aliquot of venous blood with a comparable amount of plasma was intended to decrease the red blood cell mass without altering the total blood volume. Improvement was observed after therapy was instituted.

SUMMARY

Two cases are reported demonstrating abnormally high erythrocyte values in the neonatal period associated with anorexia, lethargy, cyanosis, and convulsions. The clinical signs subsided after the infants were bled and given plasma infusions. Possible mechanisms associated with this abnormality and the rationale of treatment are discussed.

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BONE MARROW STUDIES IN THE NEWBORN INFANT AT HIGH ALTITUDES

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PREVIOUS studies of the bone marrow in the newborn infant at sea level have demonstrated an erythropoietic hyperactivity which decreases considerably on the eighth day after birth.[1-3] This increased erythropoiesis at the time of birth has been attributed to the condition of anoxia in which the fetus lives during the last periods of pregnancy. On the other hand, the depression in the bone marrow activity, observed a few days later, has been explained by the change from the anoxic fetal life to one in which oxygen is supplied normally.

It has been demonstrated that men living at high altitudes show a hyperplasia of the erythropoietic system.[4] Theoretically, a fetus in this environment must be subjected to a higher degree of oxygen deficiency because of the hypoxia existing in the maternal blood and tissues. In addition, at birth, the transition does not mean a complete reversal of the anoxic condition because of the decreased partial pressure of oxygen in the inspired air. We have thought, therefore, that it would be of interest to study the bone marrow of the newborn infant in the high altitudes.

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METHODS

Two groups of newborn infants and babies were studied: (1) nine newborn infants of normal pregnancy, from healthy mothers of the Indian race, of whom four were born in Morococha at an altitude of 4,540 meters (14,900 feet), and five in Oroya at 3,730 meters (12,240 feet); and (2) nine infants, 7 to 8 days old, of whom four were born in Morococha and the other five in Oroya.

Bone marrow was obtained by sternal puncture at the level of the manubrium with a size 20 Osgood needle. In each case approximately 0.2 c.c. of tissue was obtained and used in two smears. One smear, wet, was stained with supravital stain and the other, dry, was stained with Wright's solution. For the classification of the cellular elements, we used the nomenclature of Sabin and Miller.[5] From 200 to 400 cells were counted in each case in order to make the corresponding myelogram. Hemoglobin determinations were carried out in the Evelyn Photoelectric Colorimeter and the number of reticulocytes were determined by the technique of Dameshek.[6]

For comparative purposes, we have included in the present report previous observations made by us in 20 newborn infants and 20 8-day-old babies at sea level (Tables I and II).

The techniques used in the previous investigation were similar to those employed in the present study.

RESULTS

The macroscopic appearance of the tissue samples obtained by biopsy in the newborn infants and babies at high altitudes was characterized by the small size of the medullary clots. In contrast, the clots in the adults are larger and thicker. The microscopic examination showed a marked cellularity in the newborn infant. This was less accentuated in the babies. These findings are similar to those obtained in the previous observations at sea level. However, it is not possible to conclude, in the absence of a quantitative measurement, whether there were differences between the total number of cells in the newborn infant

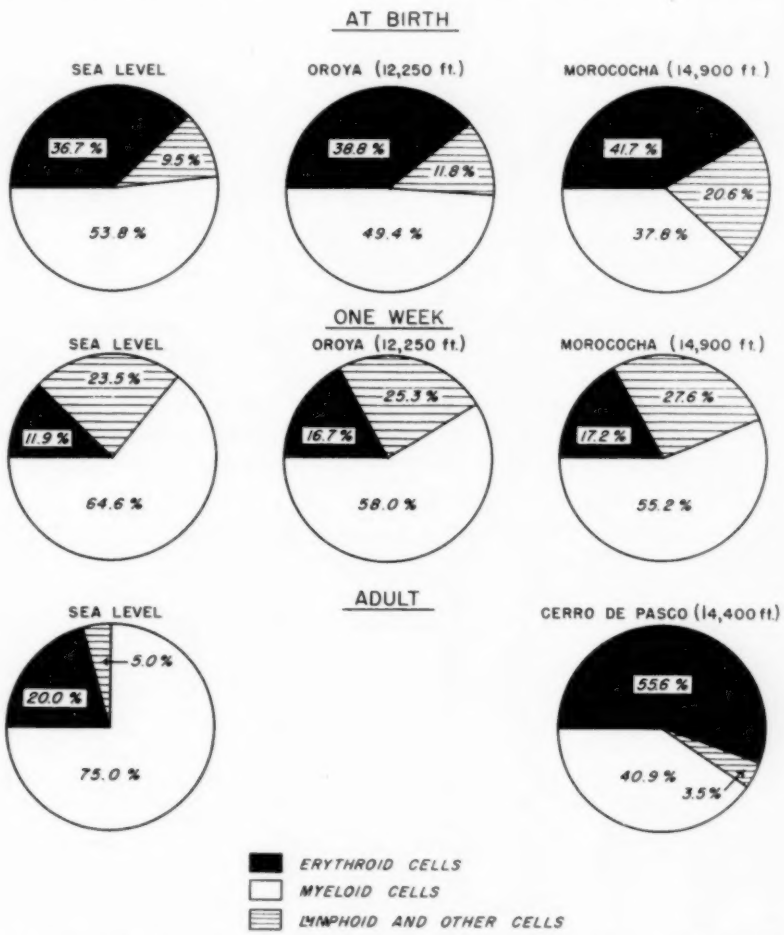

Fig. 1.—Percentage distribution of bone marrow cells at sea level and at high altitudes at various periods of life.

TABLE I. DIFFERENTIAL CELL COUNT IN BONE MARROW SAMPLES

CASE	SEX	NEUTROPHILS						EOSINOPHILS		BASOPHILS	
		SEGMENTED	BAND FORM	META-MYELOCYTES	MYELOCYTES C	MYELOCYTES B	MYELOCYTES A	SEGMENTED	MYELOCYTES	SEGMENTED	MYELOCYTES
1	F	5.4	5.4	22.2	18.4	6.3	1.1	1.2	1.2	0.0	0.4
2	M	4.0	5.4	24.3	18.2	0.3	2.0	0.9	0.0	0.0	0.0
3	F	2.1	5.5	20.7	19.3	2.0	2.0	3.4	1.3	0.0	0.0
4	F	7.4	11.3	21.5	9.8	2.5	0.3	0.0	0.0	0.3	0.0
5	F	4.8	9.0	17.3	18.4	0.6	0.3	0.6	0.3	0.6	0.0
6	M	5.0	5.0	17.3	15.0	1.2	0.3	0.5	0.9	0.3	0.0
7	M	4.5	7.4	22.3	16.8	1.0	0.4	0.3	0.3	0.3	0.6
8	F	4.3	7.7	24.5	24.5	0.4	0.3	2.5	0.8	0.8	0.8
9	M	11.1	6.9	14.6	14.2	1.5	0.6	1.5	0.0	0.3	0.3
10	F	3.9	5.0	16.6	17.8	4.1	1.2	0.6	1.5	0.0	0.0
11	F	6.5	8.0	11.5	9.0	1.5	0.7	4.0	1.0	0.4	0.2
12	F	6.5	10.0	14.3	13.8	0.3	0.3	2.2	2.6	0.0	0.0
13	F	4.6	6.0	25.2	15.5	2.5	0.0	3.2	2.2	0.0	0.0
14	M	9.4	10.0	14.4	10.0	1.3	0.6	1.1	2.2	0.0	0.0
15	F	6.5	16.3	19.3	14.9	3.5	1.8	0.0	0.3	0.3	1.6
16	F	5.9	8.0	19.3	11.3	1.4	0.3	0.0	1.4	0.0	0.0
17	F	4.2	5.6	14.0	12.9	1.4	1.9	1.5	0.5	2.5	0.2
18	M	6.4	13.4	20.5	11.0	2.3	1.0	0.0	0.0	0.4	0.4
19	M	4.8	9.8	15.4	14.2	1.5	0.3	1.2	2.2	2.8	1.2
20	M	9.4	10.3	10.3	15.5	2.3	0.9	0.7	0.7	0.0	0.0
Mean		5.15	7.8	18.7	15.3	1.43	0.86	1.32	0.93	0.14	0.28
±S.E.		±0.75	±0.53	±0.37	±0.84	±0.33	±0.14	±0.30	±0.12	±0.40	±0.10

TABLE II. DIFFERENTIAL CELL COUNT IN BONE MARROW

CASE	SEX	NEUTROPHILS						EOSINOPHILS		BASOPHILS	
		SEGMENTED	BAND FORM	META-MYELOCYTES	MYELOCYTES C	MYELOCYTES B	MYELOCYTES A	SEGMENTED	MYELOCYTES	SEGMENTED	MYELOCYTES
1	M	10.5	7.3	24.2	23.3	4.7	0.9	0.0	1.4	0.0	0.0
2	F	12.1	14.7	20.0	15.3	2.2	0.4	2.2	2.2	0.0	0.0
3	M	6.5	14.0	25.5	24.5	2.0	0.5	4.5	3.0	0.0	0.1
4	F	7.6	6.2	27.6	13.3	2.9	1.0	0.5	0.0	0.5	0.0
5	F	5.1	4.3	17.8	24.8	6.0	0.0	6.8	0.0	2.6	2.6
6	F	12.5	5.4	21.6	20.3	4.1	1.4	1.4	0.5	0.0	0.0
7	M	4.5	8.0	26.8	27.7	0.9	0.4	1.8	0.9	0.9	4.5
8	F	8.5	12.8	18.3	14.5	1.8	0.0	0.3	0.0	0.0	0.0
9	F	2.3	5.9	21.3	20.6	0.0	0.7	0.0	1.8	0.3	0.3
10	M	11.4	9.6	23.7	15.0	2.3	0.8	1.2	0.8	0.0	0.0
11	M	1.5	7.0	23.5	15.0	1.5	2.0	0.0	2.0	0.5	0.0
12	M	2.5	5.5	21.0	21.5	6.5	2.0	0.0	2.5	0.0	0.5
13	F	1.5	4.5	19.0	23.5	11.0	6.5	1.5	0.5	0.0	0.0
14	M	5.5	7.5	26.0	15.5	3.5	3.0	2.0	2.0	0.5	0.0
15	F	1.5	6.0	25.0	16.0	7.5	2.5	0.5	3.0	0.0	0.0
16	M	3.5	6.5	27.5	25.0	4.5	1.0	1.5	0.5	0.0	0.5
17	F	6.0	6.5	20.0	16.5	3.5	1.0	2.0	2.0	0.0	1.0
18	F	1.5	3.5	22.0	20.0	6.5	2.0	1.5	2.5	0.5	1.0
19	M	5.5	9.0	11.5	13.5	7.5	0.5	2.0	2.0	0.0	0.0
20	F	5.0	8.0	19.5	20.5	6.0	3.0	0.0	2.0	0.0	0.5
Mean		5.7	7.6	22.1	19.3	4.2	1.4	1.5	1.5	0.3	0.6
±S.E.		±0.81	±0.69	±0.88	±1.00	±0.61	±0.32	±0.38	±0.22	±0.13	±0.25

OBTAINED IN TWENTY NEWBORN INFANTS AT SEA LEVEL

						NUCLEATED RED BLOOD CELLS				
MYELOBLASTS	MONOCYTES	LYMPHOCYTES	CLASMATOCYTES	MEGAKARYOCYTES	PLASMA CELLS	NORMOBLASTS	LATE ERYTHROBLASTS	EARLY ERYTHROBLASTS	MEGALOBLASTS	TOTAL NUCLEATED R.B.C.
0.8	0.0	13.8	0.0	0.0	0.0	16.1	5.4	1.4	0.0	22.9
0.0	0.3	6.3	0.6	0.0	0.0	30.0	6.3	2.3	0.0	38.6
2.0	0.0	10.3	0.0	0.0	0.0	21.4	7.6	1.4	0.0	30.4
0.0	0.0	6.6	0.0	0.0	0.0	24.4	8.3	5.2	2.4	40.3
0.0	0.0	4.5	0.6	0.0	0.0	34.6	5.1	3.6	0.0	43.3
0.9	0.0	8.6	0.0	0.3	0.0	31.7	5.6	2.7	0.0	40.0
0.3	1.0	12.3	0.0	0.0	0.0	22.9	5.5	4.0	0.0	32.4
0.0	1.6	12.2	0.8	0.0	0.0	12.7	4.0	2.0	0.0	18.7
0.3	0.0	9.3	0.6	0.0	0.0	29.8	4.9	4.4	0.0	39.1
0.0	0.6	7.0	0.0	0.0	0.0	29.0	6.1	3.3	0.0	38.4
0.2	0.0	0.4	8.5	0.3	0.0	0.0	32.6	6.1	7.0	1.5	47.2
0.0	0.0	0.3	13.2	0.0	0.0	0.0	29.0	5.4	1.9	0.0	36.3
0.0	0.0	0.0	10.3	0.4	0.0	0.0	21.5	5.7	1.4	0.4	29.0
0.0	0.0	0.0	6.4	0.0	0.0	0.0	35.4	6.7	2.2	0.0	44.3
1.6	0.0	0.0	12.8	0.0	0.0	0.0	27.4	9.1	2.1	0.0	38.6
0.0	0.0	0.0	7.7	0.0	0.7	0.0	32.3	9.0	2.0	0.7	44.0
0.2	0.0	0.0	9.9	0.2	0.2	0.0	31.3	7.6	5.3	0.8	45.2
0.4	0.4	0.7	9.0	0.4	0.0	0.0	22.7	9.1	1.3	0.4	33.5
1.2	0.0	0.0	6.9	0.9	0.0	0.0	26.9	6.3	6.0	0.0	38.9
0.0	0.0	0.0	2.8	0.0	0.0	0.0	30.4	4.0	3.5	0.0	37.9
0.28	0.21	0.22	8.91	0.24	0.06	0.0	27.15	6.09	3.2	0.22	36.66
±0.10	±0.11	±0.09	±0.37	±0.06	±0.03	±0.0	±0.83	±0.47	±0.35	±0.14	±1.90

SAMPLES IN TEN INFANTS, 1 WEEK OLD, AT SEA LEVEL

						NUCLEATED RED BLOOD CELLS				
MYELOBLASTS	MONOCYTES	LYMPHOCYTES	CLASMATOCYTES	MEGAKARYOCYTES	PLASMA CELLS	NORMOBLASTS	LATE ERYTHROBLASTS	EARLY ERYTHROBLASTS	MEGALOBLASTS	TOTAL NUCLEATED R.B.C.
0.0	1.8	19.5	0.0	0.0	0.0	7.8	0.9	0.0	0.0	8.7
0.9	0.4	16.4	0.0	0.0	0.0	9.4	2.6	1.3	0.0	13.3
0.1	0.0	19.0	0.0	0.0	0.0	5.0	0.5	0.0	0.0	5.5
0.0	3.3	29.0	0.0	0.0	0.0	6.6	1.0	0.5	0.0	8.1
2.6	0.0	15.5	0.0	0.0	0.0	6.0	6.0	2.5	0.0	14.5
0.0	0.5	21.6	0.0	0.0	0.5	5.5	3.3	1.4	0.0	10.2
4.5	1.3	11.2	0.0	0.0	0.9	8.5	2.2	0.0	0.0	10.7
0.0	0.0	22.2	0.3	0.5	0.0	12.1	4.1	1.9	0.0	18.1
0.3	0.0	20.2	0.0	0.7	0.3	16.5	4.4	5.0	0.7	26.6
0.0	0.7	21.0	0.0	0.0	0.0	11.0	1.7	0.0	0.0	12.7
0.0	0.5	0.0	29.0	2.0	0.0	0.0	13.5	0.5	1.5	0.0	15.5
0.5	2.5	0.0	20.0	0.0	1.0	0.5	10.5	3.0	0.5	0.0	14.0
0.0	0.5	0.0	21.0	2.0	0.0	1.5	7.0	0.0	0.0	0.0	7.0
0.0	0.5	1.5	21.0	1.5	0.0	0.5	9.0	0.5	0.0	0.0	9.5
0.0	2.5	0.0	22.5	4.5	0.0	0.5	7.5	1.0	0.5	0.0	9.0
0.5	0.5	0.0	16.0	2.5	0.5	0.5	7.5	1.5	0.5	0.0	9.5
1.0	2.0	2.0	29.5	0.5	0.0	0.5	6.0	1.0	0.0	0.0	7.0
1.0	0.5	0.0	17.5	3.5	0.0	1.0	13.5	1.0	2.0	0.0	16.5
1.0	0.0	1.0	25.5	5.0	0.0	1.0	12.5	2.5	1.0	0.0	16.0
0.5	1.0	1.5	24.5	1.5	0.0	1.0	4.5	0.5	1.0	0.0	6.0
0.6	0.7	0.7	21.1	1.2	0.1	0.4	9.0	1.9	1.0	0.03	11.9
±.25	±0.18	±0.21	±1.06	±0.36	±0.02	±0.1	±0.73	±0.37	±0.27	±0.03	±1.13

TABLE III. DIFFERENTIAL CELL COUNT IN BONE MARROW SAMPLES

CASE	SEX	NEUTROPHILS						EOSINOPHILS		BASOPHILS		MYELOBLASTS
		SEGMENTED	BAND FORM	METAMYELOCYTES	MYELOCYTES C	MYELOCYTES B	MYELOCYTES A	SEGMENTED	MYELOCYTES	SEGMENTED	MYELOCYTES	
Morococha												
1	F	2.7	3.8	10.5	15.0	4.2	2.0	1.0	0.8	0.0	0.0	0.0
2	M	3.5	7.0	6.0	8.5	5.5	0.5	0.5	2.0	0.0	0.5	0.0
3	M	2.5	2.5	12.0	13.0	3.5	2.5	0.0	1.0	0.0	0.0	0.5
4	M	3.0	4.0	10.0	13.5	3.5	1.5	1.0	2.0	0.0	0.0	1.0
Mean		2.94	4.31	9.63	12.5	4.19	1.63	0.62	1.44	0.0	0.13	0.37
±S.E.		±1.00	±0.96	±1.27	±1.4	±0.46	±0.13	±0.23	±0.33	±0.0	±0.08	±0.24
Oroya												
1	M	5.5	12.5	11.5	17.5	3.5	1.5	1.0	0.5	0.0	0.0	1.5
2	F	5.0	8.5	16.0	13.0	3.5	1.5	1.0	0.0	0.0	0.5	0.5
3	F	3.0	6.0	20.5	16.5	7.5	3.0	1.0	1.0	0.0	0.5	0.5
4	M	5.0	5.0	10.0	9.5	4.5	1.5	2.0	2.0	0.0	0.0	1.5
5	M	4.5	7.6	13.1	10.3	2.8	1.4	0.7	0.7	0.0	0.0	0.4
Mean		4.60	7.92	14.22	13.36	4.36	1.78	1.44	0.84	0.0	0.20	0.88
±S.E.		±0.43	±1.29	±1.89	±1.60	±0.82	±0.30	±0.22	±0.33	±0.0	±0.12	±0.30

TABLE IV. DIFFERENTIAL CELL COUNT IN BONE MARROW SAMPLES

CASE	SEX	NEUTROPHILS						EOSINOPHILS		BASOPHILS		MYELOBLASTS
		SEGMENTED	BAND FORM	METAMYELOCYTES	MYELOCYTES C	MYELOCYTES B	MYELOCYTES A	SEGMENTED	MYELOCYTES	SEGMENTED	MYELOCYTES	
Morococha												
1	M	4.4	6.1	13.2	9.7	3.3	2.2	1.1	5.5	0.0	0.0	0.0
2	F	8.3	6.5	22.3	12.8	5.3	1.8	0.3	1.3	0.0	0.0	0.0
3	F	6.0	11.0	15.0	13.5	9.0	2.5	0.5	0.5	0.0	0.5	0.5
4	F	3.7	8.5	14.3	14.7	11.0	2.5	0.8	1.0	0.0	0.0	1.5
Mean		5.6	8.0	16.2	12.68	7.15	2.25	0.66	2.07	0.0	0.13	0.5
±S.E.		±1.00	±1.00	±3.92	±1.91	±1.74	±0.16	±0.31	±1.15	±0.0	±0.13	±0.35
Oroya												
1	M	3.0	10.7	17.5	16.0	6.5	1.0	1.5	0.5	0.5	0.0	0.0
2	F	3.5	8.0	13.0	12.0	10.5	4.0	0.0	0.5	0.0	0.5	1.5
3	M	6.0	5.8	17.0	18.5	7.7	5.3	2.5	2.2	0.0	0.0	0.5
4	M	5.0	3.0	9.5	13.5	13.0	7.5	0.0	1.5	0.0	0.0	2.0
5	F	2.7	5.7	16.6	16.6	8.7	4.3	1.0	1.0	0.7	1.0	1.3
Mean		4.04	6.60	14.72	15.32	9.28	4.42	1.00	1.14	0.24	0.34	1.06
±S.E.		±0.57	±0.90	±0.77	±1.10	±1.13	±1.05	±0.15	±0.10	±0.14	±0.20	±0.35

at high altitudes and at sea level. We did not have a satisfactory method available for the cell count per given volume of marrow. For this reason, our comparative criteria are based on the differential count of the cells (myelogram), expressed in percentage, a procedure employed universally in spite of its limitations. The results obtained for the qualitative and percentage distributions of the bone marrow cells in the newborn infants and babies at high altitudes are given in Tables III and IV. Because of the significant variation in altitude between Morococha and Oroya, the data corresponding to these two places are presented separately (Tables III and IV). The data corresponding to the sea level studies are given in Tables I and II.

As shown by the percentage of nucleated red cells, which was 38.8 ± 1.23 per cent in Oroya at 3,730 meters

OBTAINED IN NINE NEWBORN INFANTS AT HIGH ALTITUDE

MONOCYTES	LYMPHOCYTES	CLASMATOCYTES	MEGAKARYOCYTES	RETICULUM CELLS	PLASMA CELLS	NUCLEATED RED BLOOD CELLS				
						NORMOBLASTS	LATE ERYTHROBLASTS	EARLY ERYTHROBLASTS	MYELOBLASTS	TOTAL NUCLEATED R.B.C.
(14,900 Feet)										
0.5	17.2	0.3	0.0	0.2	0.0	31.3	7.7	2.0	0.8	41.8
0.0	22.0	0.0	0.0	0.5	0.0	36.5	5.5	1.0	0.5	43.5
1.5	20.5	0.0	0.0	0.5	0.0	28.5	9.5	1.5	0.5	40.0
0.5	15.5	0.5	1.0	1.5	0.0	27.0	10.0	3.0	1.5	41.5
0.63	18.81	0.19	0.25	0.69	0.0	30.81	8.18	1.87	0.81	41.69
±0.31	±1.49	±0.11	±0.26	±0.27	±0.0	±3.1	±0.4	±1.0	±0.23	±0.67
(12,240 Feet)										
1.0	13.5	0.0	0.0	0.0	0.0	19.5	8.5	2.5	0.0	30.5
0.0	4.5	0.5	0.5	1.5	0.0	29.0	11.0	2.0	1.5	43.5
0.5	6.0	1.0	0.0	2.0	0.0	14.5	10.5	4.0	2.0	31.0
1.0	9.5	1.5	0.0	1.0	0.5	23.0	17.5	4.0	1.0	45.5
2.1	9.6	1.4	0.7	1.0	0.0	33.7	7.9	1.4	0.7	43.7
0.85	8.62	0.88	0.24	1.10	0.10	23.93	11.08	2.76	1.04	38.80
±0.34	±1.57	±0.30	±0.12	±0.33	±0.10	±3.42	±1.73	±0.55	±0.34	±1.23

OBTAINED IN EIGHT INFANTS, ONE WEEK OLD, AT HIGH ALTITUDES

MONOCYTES	LYMPHOCYTES	CLASMATOCYTES	MEGAKARYOCYTES	RETICULUM CELLS	PLASMA CELLS	NUCLEATED RED BLOOD CELLS				
						NORMOBLASTS	LATE ERYTHROBLASTS	EARLY ERYTHROBLASTS	MEGALOBLASTS	TOTAL NUCLEATED R.B.C.
(14,900 Feet)										
1.6	34.4	1.6	0.0	0.5	1.6	11.5	3.3	0.0	0.0	14.8
0.5	21.3	0.3	0.0	0.0	0.0	16.8	2.5	0.0	0.0	19.3
0.5	25.0	1.0	0.0	1.0	0.0	10.5	1.5	1.5	0.0	13.5
1.0	16.2	1.0	0.5	1.7	0.3	15.5	5.2	0.5	0.0	21.2
0.90	24.23	0.97	0.13	0.81	0.46	13.57	3.14	0.5	0.0	17.20
±0.61	±3.83	±0.37	±0.13	±0.37	±0.38	±0.57	±0.78	±0.35	±0.0	±1.83
(12,250 Feet)										
0.5	24.5	0.0	0.0	1.0	0.0	13.5	2.0	2.5	0.0	18.0
3.0	24.5	1.0	0.5	3.0	1.0	9.5	1.0	3.0	0.0	13.5
1.5	15.0	1.0	0.3	0.5	0.0	12.7	3.0	1.0	0.0	16.8
1.0	24.0	1.5	0.5	1.5	0.5	14.0	1.5	0.5	0.0	16.0
1.3	19.6	1.0	0.3	0.3	0.0	16.7	2.7	0.0	0.0	19.4
1.40	21.40	0.90	0.32	1.26	0.30	13.28	2.04	1.40	0.0	16.74
±0.45	±2.14	±0.24	±0.08	±0.40	±0.20	±1.16	±0.37	±0.43	±0.0	±0.88

and 41.7 ± 0.67 per cent in the higher locality of 4,540 meters, an erythropoietic hyperactivity was observed in the newborn infant at high altitudes. These values were slightly higher than the value of 36.7 ± 1.90 per cent observed by us in the newborn infant at sea level, moderately higher than the percentage (32 per cent) obtained by Shapiro and Bassen,[2] but almost similar to the one (40 per cent) found by Gairdner and associates.[3] All these observations were made at sea level. With regard to the maturation of the erythroid cells in the newborn infant at high altitudes, we can point out the predominance of normoblasts. Erythroblasts, most of them mature with some young erythroblasts, a few megaloblasts, and a moderate number of cells in mitosis were also observed. All these characteristics were entirely similar to those found in the newborn infant at sea level. Finally, the degree

of reticulocytosis, which corresponds to the peripheral index of the erythropoietic activity, was similar in the newborn infant at the three altitudes: Morococha (4,540 meters), 3.6 ± 0.26 per cent; Oroya (3,730 meters), 3.2 ± 0.70 per cent; and in Lima (sea level), 3.5 ± 0.07 per cent.

In the samples taken one week after birth there was a marked decrease in the nucleated red cells, the mean being 16.7± 0.88 per cent in Oroya and 17.2 ± 1.87 per cent in Morococha. However, this decrease was less accentuated than the one observed at sea level where the corresponding value for babies of the same age was 11.9 ± 1.13 per cent.

The difference in results for babies between sea level and high altitudes may be better appreciated from the fact that the concentration of nucleated red cells in Oroya and Morococha was 40 and 44 per cent, respectively, values higher than those at sea level.

Simultaneously with the decrease in the erythroid cells of the bone marrow, there was a decrease in the reticulocytes of the peripheral blood which reached adult levels after 1 week of life, both at sea level and at high altitudes.

All these observations indicate that even at high altitudes, where the environmental oxygen pressure is decreased, a depression of the erythropoietic activity occurs after birth, although this process is not as marked as at sea level.

The myeloid cells presented a normal morphology in the newborn infant at high altitudes with no increase in the young elements. The percentage of the myeloid cells increased, after the first week of birth, from 37.8 to 55.2 per cent in Morococha and from 49.4 to 58.0 per cent in Oroya. This increase, also evident in the newborn infant at sea level, is probably of a relative nature, due to the decrease in the erythroid cells which occurs at this period of life. This is associated with a reduction in the granulocytes of the peripheral blood, both at sea level and at high altitudes.[1, 2, 7-9] In the absence of a peripheral demand, it is difficult to accept as an actual occurrence the more accentuated granulopoietic activity in the bone marrow.

The difference in behavior between the erythroid and myeloid cells in this early period of life should be emphasized. The difference suggests that the anoxic stimulus, which has an important stimulating influence on the production of red cells, lacks such action on the formation of the granulocytic series, a fact already pointed out by Hurtado[10] and Barcroft and associates.[11]

The percentage of 18.9 ± 1.49 per cent for the cells of the lymphoid series, found in the bone marrow of the newborn infant at the highest locality, was higher than the one found in the lower one (Oroya) (8.6 ± 1.57 per cent) and at sea level (8.9 ± 0.37 per cent). In all groups, an appreciable elevation occurred on the eighth day of life: Morococha, 24.2 ± 3.8 per cent; Oroya, 21.4 ± 2.14 per cent; and Lima, 21.1 ± 1.06 per cent. This phenomenon is associated with a simultaneous increase of these cells in the peripheral blood.[1, 8, 9] It is difficult to interpret the elevated number of lymphoid cells at the highest altitude. However, this finding is in agreement with the lymphocytosis demonstrated by Loret de Mola[8] in the peripheral

blood of the newborn infant at high altitudes.

The cells of the megakaryocytic series showed normal characteristics in their morphology and percentage distribution both at sea level and at high altitudes.

Data concerning hemoglobin determinations at birth, at sea level and high altitudes, are given in Table V.

TABLE V. HEMOGLOBIN OBSERVATIONS IN NEWBORN INFANTS AT DIFFERENT ALTITUDES

PLACE	ALTITUDE (FEET)	NUMBER OF CASES	HEMOGLOBIN (GRAMS PER 100 C.C.)	
			MEAN	STANDARD DEVIATION
Lima	Sea level	23	15.4	1.30
Oroya	12,250	23	16.0	1.54
Morococha	14,900	9	16.8	2.57

It can be seen that the mean value is slightly higher in the Oroya group (16 Gm. per 100 c.c.) than in the sea level group. The difference between the Morococha group (16.5 Gm. per 100 c.c.) and the sea level one is still higher; but in both cases the differences have no statistical significance.

DISCUSSION

The oxygen saturation of the arterial blood in adults living at high altitudes is lower than at sea level.[10, 11] In Morococha and in Oroya, where our observations have been carried out, arterial oxygen saturation has the mean values of 81.0 and 86.6 per cent, respectively. It is then logical to assume that the provision of oxygen by the mother to the fetus in utero does not have the same efficiency as at sea level. In consequence, the newborn infant should show at high altitudes a greater erythropoietic activity than at sea level. However, the observations presented in this report indicate that such a process is not significantly different in the newborn infant at high altitudes when compared with the newborn infants at sea level. The percentage difference of nucleated red cells in the bone marrow of the newborn infants in Oroya and Lima has no statistical significance and, although this value is slightly higher in Morococha, the variation is also insignificant. Also, it is evident that the degree of reticulocytosis is about the same in Lima as in the two localities at high altitudes. These observations demand a brief consideration of the possible factors responsible for the lack of response in the erythropoietic activity of an infant born of an hypoxic mother.

One of these factors could be related to the deviation to the right of the oxygen dissociation curve in the maternal blood, thus facilitating the delivery of oxygen to the placenta at low levels of oxygen pressure. Such deviation has been described to occur at sea level in the maternal blood in the late period of pregnancy.[12] A similar change has been found in the blood of adult males living at high altitudes.[13] It would be interesting to carry out similar investigations in the blood of pregnant women at high altitudes in order to evaluate the influence of this factor in the transport of oxygen to the fetus.

An investigation, now in progress, concerning the position of the oxygen dissociation curve in the newborn infant and in the pregnant mother at

high altitudes will contribute to the understanding of this problem.[14]

The total volume of circulating red cells at the time of birth may be another regulating factor of the erythropoiesis. Loret de Mola[8] has observed an increase in the number of red cells and in the quantity of hemoglobin in the circulating blood of the newborn infant in Oroya and Morococha. However, the number of cases studied was small and the variability in the results relatively high. Our mean values for blood hemoglobin in the newborn infants of Morococha and Oroya, carried out in a larger group, have shown a less accentuated difference between high altitude and sea level subjects, but this is also without statistical significance (Table V). In addition, no observations on the total blood volume have been made in the newborn infant and babies at high altitudes in order to know, conclusively, whether or not we are dealing with an absolute increase in the red cell mass. If an increase in the red cell mass is demonstrated, the increase could be interpreted as one of the factors preventing the accentuation of erythropoietic activity in the bone marrow tissue. One must also take into consideration other factors, the role of which is not known at high altitudes, related to the possible humoral, endocrine, and enzymatic control of erythropoiesis, and which may play an important role at birth. The thickness of the placenta tissue could be another factor. If the placenta at high altitudes is thinner than at sea level, oxygen diffusion is more facilitated.

Another finding which deserves consideration is the depression of erythropoiesis which has been observed one week after birth both at sea level and at high altitudes. This depression is possibly related to the fact that at birth the fetus passes from a medium of decreased oxygen supply to one in which oxygen supply is adequate, thus eliminating the stimulation present up to that moment. At high altitudes this phenomenon is also operating, although at a lower degree of intensity because of the decrease in the partial pressure of oxygen in the inspired air. It must be also pointed out that the changes in the peripheral blood found one week after birth, and which have been also observed by Loret de Mola[8] at high altitudes, are not exclusively dependent on a decreased cell production, but are also related to a reduction in the life span of the red cells in this period of life. As we have demonstrated,[15] this phenomenon is present at high altitudes.

The fact that the depression of the erythropoietic activity in the bone marrow of infants at high altitudes is not as accentuated as at sea level would indicate that in this environment there is a constant demand for the best possible oxygen transport as an important adaptative mechanism. It would be highly interesting to perform bone marrow studies at different age periods at high altitudes in order to observe the changes which gradually will lead to the increased erythropoietic activity observed in adult subjects living at high altitudes.[4] In these subjects, the percentage (55 per cent) of nucleated red cells in the bone marrow is even higher than at the moment of birth.

SUMMARY

Studies have been made of the bone marrow in 9 newborn infants and in

8 infants 1 week old, at the altitudes of 4,540 meters (14,900 feet) and 3,730 meters (12,240 feet). A comparative study has been made with previous observations, of a similar nature, carried out by us at sea level. Hyperplasia of the erythroid cells was found but the degree was no greater than the one observed at sea level. No changes were evident in the myeloid and megakaryocytic cell series.

An inhibition of the erythropoietic activity was found one week after birth. This process was moderately more accentuated at sea level than at high altitudes.

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Foreign Bodies in Bladder

M. Denucé (Moniteur des Hôpitaux) has collected the particulars of 391 published cases, and the enumeration he gives of the bodies in question is both curious and useful. In 78 there were portions of catheters or lithotrity instruments, viz., 15 metallic catheters, 9 gum-elastic catheters, 7 gutta percha catheters (a large proportion, considering the short time these dangerous instruments have been in use), 28 catheters (their nature not being specified), 16 bougies, and 3 branches of *brisepierres*. Then we have 82 needles, pins, or tags, 1 stiletto, 1 crochet-needle, 6 bone or ivory needles, 6 ear picks, 3 ivory whistles, 1 ivory spindle, 1 ivory stiletto handle, 15 leaden balls, 3 small keys, and 8 instances of metallic fragments of various kinds. In 12 bones or splinters of bone, in 10 pebbles or china, 6 pen-holders, 15 needle-cases, 10 pieces of tobacco pipe, 4 portions of glass tubes. In 21 instances fragments of wood, as 3 pencils, 1 piece of a match, 1 ramrod, 1 mustard-spoon handle, &c. In 34 there were fragments of plants, as ears of corn, stalks, &c.; in 26, fruits or kernels; in 4, tents of charpie, 1 strip of linen, 1 skein of cotton, 3 débris of cotton or wool, 2 pieces of cord, 4 portions of wax candle, 3 pens, 1 piece of whalebone, 2 leather bootlaces, 1 piece of tendon, 2 débris of fecal matter, 1 pessary, 1 shell, 14 instances of various foetal débris, 6 locks of hair, 2 of larvae of insects, and in 1 pills.

From the AMERICAN JOURNAL OF MEDICAL SCIENCES, VOL. 35, 1858

INTESTINAL POLYPOSIS WITH ORAL PIGMENTATION (PEUTZ-JEGHERS SYNDROME)

Report of a Case With Review

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Providence, R. I.

IN 1896, Sir Jonathan Hutchinson[1] reported the occurrence of peculiar intraoral pigmentation in twin sisters. Parkes Weber[2] in 1919 published a follow-up study of these girls and learned that one had died of what clinically appeared to be an intussusception, and that the other had succumbed to carcinoma of the breast. He was unable to demonstrate a hereditary factor in this case.

In 1921, Peutz[3] published the case of a Dutch family, many members of which suffered from intestinal polyposis with abnormal pigmentation in and around the mouth. He established the fact that these apparently unrelated lesions constituted a rare but well-defined syndrome. Since that time, about 100 cases have appeared in the world literature. Since 1948, very few instances of this syndrome have appeared in pediatric journals.[4-9]

CASE REPORT

First Admission.—J. T., a 5-year-old white boy, entered the Roger Williams General Hospital on June 19, 1957, complaining of severe abdominal pain and vomiting.

The family history was negative except that the father was suffering from terminal bronchogenic carcinoma. There was nothing unusual in his past history.

For the past month or so the child had appeared tired and listless, his appetite was very poor, and he complained of excessive thirst. There was no history of melena or diarrhea.

On the morning of admission the child complained of severe cramplike abdominal pain with nausea and vomiting. There was no elevation of temperature.

Physical examination disclosed a pallid boy in acute abdominal distress. Except for periumbilical tenderness, the physical examination was essentially negative.

Laboratory findings: The urine showed dextrose 1 plus and acetone 4 plus.

The hemoglobin was 6.7 Gm. per cent (47 per cent). The red blood cells numbered 4,000,000 per cubic millimeter, and the white cells 19,000 per cubic millimeter. Differential count revealed bands 2 per cent, segmenters 84 per cent, lymphocytes 10 per cent, and large mononuclears 4 per cent. The red cells showed moderate hypochromia, moderate anisocytosis, poikilocytosis, and occasional polychromasia.

The blood sugar ranged from 98 to 228 mg. per cent. The glucose tolerance test showed a fasting level of 98 mg. per cent, a maximum level of 142 mg. per cent, and a terminal level of 74 mg. per cent at the end of the third hour. All corresponding urine specimens were negative to sugar.

The carbon dioxide-combining power was 29 vol. per cent, or 13.2 mEq. The plasma acetone was negative. The serum amylase was 56 mg. per cent. The blood sodium, potassium

From the Departments of Pathology and Pediatrics, Roger Williams General Hospital, Providence, R. I.

Presented before the New England Pediatric Society, March, 1958.

chlorides, and blood urea nitrogen determinations were within normal limits.

Culture of the nose and throat revealed nothing unusual.

X-ray studies of the abdomen disclosed a large, soft tissue mass in the right abdomen. There was marked distention of the small bowel attributed to obstruction.

Electrocardiographic studies were negative.

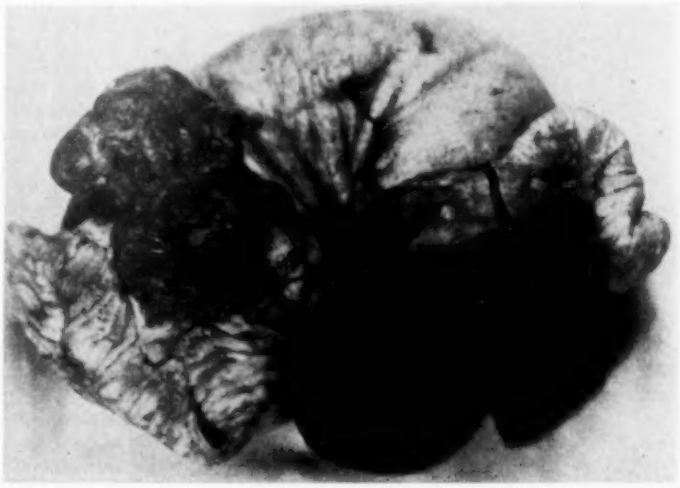

Fig. 1.—Intussuscepted segment of jejunum, with hemorrhagic polyp at one end.

At operation, performed by Dr. Bruno DiClemente, a large amount of clear serous fluid was found in the peritoneal cavity. In the mid-jejunum there was a large intussusception, bluish in color, but not gangrenous. It was irreducible and a mass interpreted as a polyp could be palpated inside. This segment of small intestine was resected and an end-to-end anastomosis was carried out.

Pathology: The specimen consisted of a loop of jejunum 30 cm. long and about 5 cm. wide, with mesentery attached. The serosal surface was mottled, livid, purple-brown in color, smooth, shiny, and glistening. Most of the specimen actually consisted of an intussusception which measured about 22 cm. in length. The intussuscepted area contained a small amount of bloody fluid. At the point of origin of the intussusception there was an elongated, pedunculated, hemorrhagic, polypoid mass (Fig. 1) which measured 4 by 3 by 1.5 cm. This mass was soft, edematous, and gangrenous in appearance. The mesenteric glands included in the specimen were somewhat enlarged and light tan-brown to purple in hue. Microscopic study of the polyp showed disorganization of histology by hemorrhage so that the picture of a polypoid adenoma was obscured. The pathologic diagnosis was jejunojejunal intussusception of the small bowel with polypoid adenoma of the jejunum.

Recovery was uneventful and the child was discharged on June 29, 1957, as improved.

Second Admission.—The patient was readmitted on Jan. 10, 1958, complaining of episodes of abdominal pain, pallor, weakness, tarry stools, and repeated attacks of upper respiratory infection.

Physical examination disclosed a very pale boy whose lips were cyanotic. At this time, numerous small blackish-purple, discrete spots were noted on

Fig. 2.—Several melanotic spots are seen on the buccal surface of the cheek.

the mucosal surface of the lower lip, the mucosal surface of the cheek, and on the hard palate (Fig. 2). Otherwise, nothing new was discovered on physical examination.

Laboratory findings: On admission, the hemoglobin was 4.5 Gm. per cent (31.6 per cent). Red blood cells numbered 1,850,000 per cubic millimeter and white blood cells 7,700 per cubic millimeter. The differential white count was normal. The red cells exhibited moderate anisocytosis, poikilocytosis, and hypochromia. The platelets were not reduced. The stools were positive for occult blood.

X-ray studies of the gastrointestinal tract showed evidence of jejunal polyposis (Fig. 3).

Three blood transfusions were given and iron therapy was started. There was considerable improvement and the patient was discharged Feb. 1, 1958, with a diagnosis of Peutz-Jeghers syndrome.

Third Admission.—The patient was observed periodically in the outpatient department and, on April 30, 1958, was readmitted to the hospital complaining of severe abdominal pain, anorexia, nausea, and vomiting.

Physical examination was unrevealing and there was neither abdominal tenderness nor rigidity.

X-ray examination showed evidence of a collection of gas in the upper midline of the abdomen, probably in a dilated small bowel, which was considered consistent with small intestinal obstruction.

Laboratory studies showed a white cell count of 20,000 per cubic millimeter. The differential count showed bands 7 per cent, segmenters 87 per cent, lymphocytes 4 per cent, and large mononuclears 2 per cent. The first hemoglobin estimation was 9.9 Gm.; later the hemoglobin was 12.6 Gm.

A diagnosis of small intestinal obstruction was made and a laparotomy was done by Dr. Joseph Caruolo. About 14 cm. from the ligament of Treitz a small polyp with an unusually long pedicle, attached to the mesenteric border, was discovered and removed. About 15 cm. distal to this site another larger polyp with a short stalk attached to the antimesenteric border was encountered and removed. After removal, this lesion shrank appreciably in size. Observation before the polypectomies showed an unmistakable dimpling suggestive of beginning intussusception at the site of the larger polyp. Just distal to this polyp a segment of jejunum about 15 cm. in length exhibited marked edema with hemorrhage into the corresponding segment of mesentery, with mesenteric lymphadenopathy. Elsewhere there were numerous adhesions from previous surgery, with one very tough adhesive band.

It was felt that these findings could be best explained on the basis of a spontaneous reduction of a jejunojejunal intussusception, although spontaneous correction of a herniation

or volvulus of a loop of gut involving the dense adhesive strand could not be excluded.

No other polyps could be palpated in the small intestine and fecal masses and concretions in the colon prevented

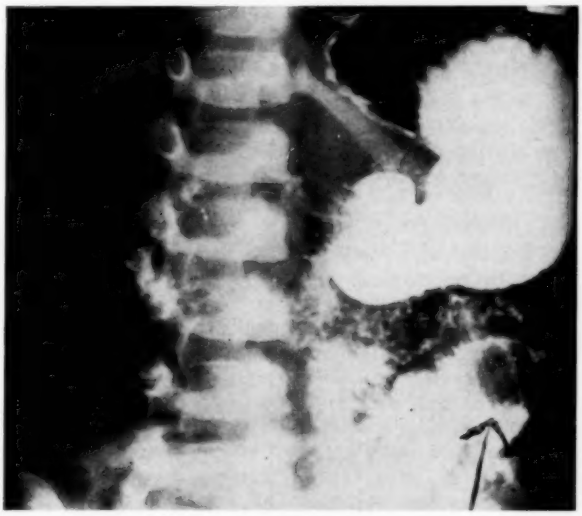

Fig. 3.—There is an ovoid filling defect in the small bowel consistent with a polyp.

Fig. 4.—Myriads of glands are separated by chronically inflamed connective tissue.

accurate examination of this portion of the bowel by palpation.

Pathology: The specimen consisted of two ovoid, mottled, grayish-purple masses of pliable tissue, each with an attached stalk, said to be jejunal polypoid adenomas. They measured 2.5 by 2 by 0.75 cm. and 4 by 3 by 1 cm., respectively. The smaller lesion presented a stalk measuring about 6 cm.; the pedicle of the larger specimen was much shorter.

Microscopic examination of both specimens showed identical pathology (Fig. 4). There were myriads of glandular spaces frequently presenting a papillary pattern, lined by a single layer of tall columnar epithelium. The stroma was moderately cellular and contained many plasma cells and eosinophils. Pathologic diagnosis was polypoid adenomas of jejunum (Peutz-Jeghers syndrome).

Recovery was uneventful and the patient was discharged May 10, 1958. He was referred to the outpatient department for periodic observation and examination.

DISCUSSION

In 1949, Jeghers, McKusick, and Katz[10] published a classical article in which the entire subject of the Peutz-Jeghers syndrome was presented. They reviewed the literature to that date and stated that a total of 21 cases had been reported. They also discussed the pathology, pathogenesis, symptoms, and hereditary factors operative in the condition.

Peutz-Jeghers syndrome is, by definition, a combination of oral melanosis combined with small intestinal polyposis, in which frequently a definite hereditary factor can be demonstrated.

Males and females are equally affected. The age at which the condition has been reported ranges between 4 and 76 years. Symptoms usually begin in the second decade.

Cases have been reported from the United Kingdom, United States, Australia, South Africa, India, Germany, France, Holland, Israel, Poland, Switzerland, Japan, Hungary, and Nigeria, and have been described in Caucasians, Negroes, Mongolians, and natives of India.

Arbitrarily, to be complete, the syndrome must present buccal, facial, or labial melanosis, associated with polyposis of the small intestine. There may or may not exist a concomitant polyposis of the stomach and/or large intestine and rectum.

Pigmentation.—This is the most striking and obvious manifestation of the syndrome and is usually found in brunets. The distribution of the melanin spots is fairly consistent and occurs most frequently on the labial and oral mucosa as ovoid to round splotches of brownish-black pigment. These areas tend to be more conspicuous on the oral mucosa, but occasionally are encountered on the gums and/or the hard palate. They are rarely seen on the tongue. On the lips they are more striking on the buccal than on the cutaneous surface and occur most frequently on the lower lip. Histologic studies of these lesions indicate that the pigment is melanin and is distributed in discrete vertical bands throughout the epidermis.

The spots on the skin are smaller, measuring about 1 mm. or less. They are more numerous around the mouth, below the nose, about the eyes, and have been reported as occurring over the nose in a butterfly pattern. The spots are most numerous near the facial

orifices. They are more sharply demarcated than freckles, remain discrete, and do not coalesce. With age they tend to disappear or, at least, to fade.

The melanotic spots may also be found on the fingers, toes, hands, and feet.

Freckles (ephelides) are easy to differentiate from these melanotic areas. Other skin discolorations to be considered in a differential diagnosis are those associated with lentigo, chloasma, xeroderma pigmentosa, von Recklinghausen's disease, and melanosis of external origin.

Intestinal Polyposis.—This is the second essential component of the syndrome, and it is generally agreed that small intestinal polyposis is a sine qua non of this condition. As a matter of fact, polyposis of the small intestine is sufficiently rare in itself to justify an intensive physical examination with the Peutz-Jeghers syndrome in mind. Lawrence,[11] in a review of 7,000 autopsies, concluded that polyposis of the large intestine is 12 times as frequent as small intestinal polypi. Ladd and Gross,[12] in a review of 92 cases of polyposis, noted polypi of the stomach and small intestine in only 2 cases.

In any given case of Peutz-Jeghers disease, there may or may not be simultaneous polyposis of the stomach and/or colon or rectum.

The polyps present the usual histopathology of polypoid adenomas of the gastrointestinal tract. By most observers, polyps are regarded as neoplasms which eventually may become malignant. However, Bartholomew, Dahlin, and Waugh[13] suggest that these lesions may be hamartomas. In any event, the tendency toward malignancy does not seem to be so marked as in hereditary colonic polyposis. According to Dormandy,[14] no case has yet been reported in which death has been unequivocally attributed to malignancy as a complication in such a polyp.

Symptoms.—Many cases are asymptomatic and are discovered only in the genetic investigation of a familial case.

The chief symptoms, when present, are gastrointestinal, and include abdominal pain, bowel obstruction from repeated or even multiple intussusceptions, melena, anorexia, and weakness. A very characteristic symptom mentioned by Dormandy[14] is the presence of explosive and extremely audible borborygmi, which may well be the cause of extreme embarrassment. Most cases, however, are first seen and hospitalized owing to fulminant symptoms of intussusception with bowel obstruction. In a minority of cases, anemia, presumably a result of slow bleeding from multiple polyps, is the presenting complaint. Some cases, like our own, present both types of complaints.

One very unusual feature, mentioned by Dormandy,[14] and which may have some diagnostic importance, is the fact that intestinal masses, presumably occasioned by intussusception, have been known to disappear as a result of massage of the abdomen.

Diagnosis.—There is perhaps no other syndrome in medicine which illustrates so vividly the value of a thorough and meticulous physical examination. Certainly many cases have been missed, either because in obscure cases of gastrointestinal disease or anemia the pigmentation is not searched for, or, if seen, is not properly

evaluated. In our case the pigmentation was noticed and correctly interpreted only on the second hospital admission, after the patient had undergone, during a previous admission, a major operation for bowel obstruction. Such pigmentation should be looked for in every case of small intestinal polyposis and, conversely, the discovery of such areas of pigmentation during physical examination should direct the attention of the clinician to the gastrointestinal tract. In a day of many complex and expensive tests and laboratory procedures, it is indeed remarkable to have one's attention directed to the focus of the trouble by discoloration visible at some distance.

The occurrence of polyps in the small intestines is sufficiently uncommon to arouse suspicion of the syndrome. From the gastrointestinal standpoint, one must differentiate between colonic polyposis, bleeding peptic ulcer, intestinal carcinoma, leiomyosarcoma, Meckel's diverticulum, and malignant lymphoma.

Heredity.—In about one half of the cases there is a demonstrable hereditary factor. The disease is said to appear as a simple mendelian dominant, with no generation skip, as the result of a single pleiotropic gene responsible for the melanosis and the polyposis. In those cases in which no hereditary factor can be demonstrated, a mutation can be assumed. However, in cases in which one must depend upon interrogation of a patient or relatives in order to elicit information concerning pigmentation in relatives not available for examination, it should be borne in mind that these discolorations are in no sense cosmetic deformities and that they may well have escaped particular observation and comment by members of the family, or by the affected individual himself. A negative family history, therefore, may be misleading in genetic surveys.

When the question arises concerning transmission of the disease to the next generation, members of an affected family who show no pigmentation may be told that their children are unlikely to suffer. Those with characteristic pigmentation can be informed that their offspring will have a 50 per cent chance of inheriting the disorder.

Treatment.—The first concern in treatment is usually the relief, by surgical removal, of the intussusception responsible for the acute bowel episode. After the diagnosis has been established, the question arises as to whether polyps demonstrated by x-ray should be removed electively. Various factors influence judgment in such a difficult decision, such as the location of the polyps, their number, distribution, and the like. Most observers believe that malignancy could eventually develop in one or more of these lesions and Berkowitz, Pearl, and Shapiro[13] believe that 9 per cent of all intestinal polyps are a part of this disorder and feel, from their review of the literature, that malignancy has been seen in about 20 per cent of these. Dormandy,[14] on the other hand, takes a more optimistic view of the situation. This observer feels that in those cases in which malignancy has been reported subsequent clinical developments have not confirmed the diagnosis. He states that no case of Peutz-Jeghers syndrome can be found in the literature in which death can be irrefutably attributed to such a malignancy. It has, furthermore, been observed in cases in which a series of intussusceptions have necessitated several laparotomies, that

polyps have developed in areas previously considered to be free of them. It can easily be envisaged that several elective prophylactic operations with a loss of enough small bowel will cause serious metabolic disturbances. It can be concluded therefore, in considering elective polypectomy, that no general rule can be laid down but that each case must be carefully and individually evaluated.

The anemia, which is the result of slow bleeding from the polyps, can be successfully treated by blood transfusions and the administration of appropriate iron compounds.

No treatment has been suggested for the melanotic areas, which are asymptomatic in themselves and are not cosmetic problems.

It has been suggested that patients afflicted with this disease, both with and without symptoms, should be thoroughly instructed concerning the nature of their trouble so that they will be in a position to impart this knowledge to future medical consultants, thereby avoiding unnecessary, expensive, and time-consuming investigations. It has also been suggested for obvious reasons that such persons have periodic hemoglobin estimations.

SUMMARY

1. A case of Peutz-Jeghers syndrome, in a 5-year-old boy, one of the youngest on record, is added to the pediatric literature.

2. The various elements that comprise this unusual symptom complex are reviewed, and various therapeutic and prophylactic measures are discussed.

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A COMPARISON OF MEPROSPAN (SUSTAINED ACTION MEPROBAMATE CAPSULE) WITH OTHER TRANQUILIZING AND RELAXING AGENTS IN CHILDREN

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IRRITABILITY, restlessness, apprehension, and sleeplessness are often difficult problems in the management of handicapped or ill children. In selected instances, administration of a tranquilizing or relaxing agent may be indicated as an adjunct to treatment of the primary condition. Although our experience[2, 3] and that of others[8, 9, 11] has indicated its relative safety and effectiveness, the use of meprobamate (Miltown) in children has been limited because of its bitter taste. Recently, capsules containing meprobamate in a sustained action form (Meprospan*) have been made available, and the granular contents of these capsules are usually accepted by young children.

The following report is a comparison of our experience over a four-year period with 210 children each of whom was treated with meprobamate and with at least one other relaxing drug. Their initial complaints included headache, sleeplessness, behavior problems, irritability or apprehension, secondary to some other disease. Many were seriously retarded in their motor or mental development, but the presence of increased muscle tone or athetoid movements was a secondary rather than a primary indication for the use of tranquilizing or relaxing agents.

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*Supplied by the Wallace Laboratories, New Brunswick, N. J.

SUBJECTS

The ages of the patients studied ranged from 2 months to 14 years. Each of the children was examined periodically either in the Cerebral Palsy Clinic or in the Medical Clinic of St. Christopher's Hospital for Children. They were selected for this study because their signs and symptoms suggested that a tranquilizing or relaxing agent might benefit them, and also because their parents were believed to be cooperative. The children can be arbitrarily divided into six groups as follows: (1) Cerebral palsy (spastic) in children with evidences of irritability, apprehension, sleeplessness or restlessness which limited their progress at home, in school, or in therapy. (2) Cerebral palsy (athetoid) in children with irritability, apprehension, sleeplessness or restlessness which limited their progress at home, in school, or in therapy. (3) Behavior disturbances in patients with evidence of mental retardation. (4) Headache in children whose mental and motor development was believed to be within the limits of normal. (5) Sleeplessness in children whose mental and motor development was believed to be within the limits of normal.

(6) "Brain injury" in children who had no definite motor handicap, but whose marked distractibility, short attention span, and erratic behavior suggested the diagnosis of a postencephalitic syndrome, although most of these children did not have a history of a previous illness. This combination of symptoms has been called "brain injury" by Strauss,[14, 15] and hyperkinetic impulse disorder by Laufer and Denhoff.[10]

The cerebral palsy patients were further divided according to their degree of severity and therapeutic requirements[13] as follows:

Degree of severity:

I (no practical limitation of activity)
II (slight to moderate limitation of activity)
III (moderate to great limitation of activity)
IV (unable to carry on any useful physical activity)

Therapeutic requirements:

A (not requiring treatment)
B (in need of minimal bracing and other minimal therapy)
C (in need of bracing and/or other apparatus and the services of a cerebral palsy treatment team)
D (limited to such a degree that long-term institutionalization and treatment are required)

METHOD

In addition to physical and neurologic examinations, appropriate laboratory studies were obtained. These included blood counts, urinalyses, electroencephalography, roentgenograms of the skull, osseous age, psychologic and developmental testing, and the like.

Initially small amounts of medication were prescribed. The dose was gradually increased until the desired effect was obtained or untoward side effects occurred. Progress reports were obtained by telephone conversations, interviews with parents, and reexaminations of most children every 2 weeks; many were seen more frequently. After a fair trial, the drug was changed whether or not the medication had proved satisfactory. Most of the children received each drug for more than two months. However, if the child tolerated the drug poorly, the medication was discontinued after a few days.

Objective measurements,[16] such as recording muscle tone and time required for certain motor acts, were carried out in selected patients. However, drug effectiveness was determined by clinical judgment and from observations by parents and therapists.

DRUGS AND DOSAGE

The four compounds evaluated in this study are described below:

Meprobamate (Miltown, Meprospan).—This agent is a propanediol derivative. In addition to its tranquilizing action, it has some anticonvulsive and muscle-relaxant properties. Following the administration of 400 mg. tablets, an effect was usually apparent in 45 minutes, reached its maximum in 90 minutes, and disappeared in 180 minutes.

The administration of meprobamate in sustained action form produced a more uniform and sustained action over a period of 6 to 8 hours.

The dose was relatively easy to adjust. For cerebral palsy children the effective dose of the capsule was between 25 and 60 mg. per kilogram per day, and for other patients between 10 and 15 mg. per kilogram per day.

Initially, meprobamate was used in tablet form. When the sustained action capsules containing meprobamate became available, some of the children were changed to them. Subsequently, others were treated exclusively with the capsular form. Of the 210 children receiving meprobamate for more than 4 days, 60 received both tablets and capsules; 47 were given only capsules. The capsules were opened and the granules mixed with ice cream, apple sauce, and other food. These were readily accepted by most children and had the additional advantage of being effective in small doses.

Promazine (Sparine).*—This phenothiazine derivative is a potent ataractic drug. However, the sedative action of promazine was considerably stronger than that of meprobamate, and it was difficult to achieve a dosage level which would quiet the child and not make him sleepy at the same time.

Promazine was available in liquid form (100 mg. per cubic centimeter). The effective dose was found to be between 50 and 400 mg. daily.

Reserpine (Rau-Sed†).—This alkaloid of rauwolfia is a potent tranquilizer which has hypotensive properties.[18] Careful dosage regulation was required which, in some instances, might take several weeks of manipulation. Once an effective dose is reached, the child could usually be maintained at the same level.

Reserpine was used as a syrup (4 mg. per teaspoon) and as a tablet (4 mg. per tablet). In most instances, the initial dose of 2 mg. three times a day was increased at weekly intervals until the patient was stabilized on the drug. Large amounts (10 to 16 mg. per day) were sometimes needed to obtain the desired response.

Zoxazolamine (Flexin).*—This is a long-acting spinal cord depressant. Its main indication is for patients in whom there is a marked increase in muscle tone. Some of the children who tolerated the drug could be more easily dressed and fed, and generally appeared to be more comfortable. However, the administration of zoxazolamine was often associated with gastric upsets and other untoward side effects.[19]

This drug was available in tablets of 250 mg.; the effective dosage varied from 30 to 140 mg. per kilogram per day in divided doses.

RESULTS

The over-all effectiveness of these four compounds in relieving symptoms for which they were prescribed appears in Table I. Of the 210 patients, 109 (52 per cent) showed the greatest improvement on meprobamate, and 59 (28 per cent) responded better to one of the other drugs; 42 (20 per cent) derived no benefit from drug treatment.

"Best response" indicates that the patient improved following the administration of a drug, and that one drug seemed better than any of the other agents employed. It does not mean that all of the presenting symptoms disappeared or that underlying defects such as mental retardation were altered.

SIDE EFFECTS

Meprobamate.—There were no serious side effects, although drowsiness

*Supplied by Wyeth Laboratories, Philadelphia, Pa.

†Supplied by E. R. Squibb & Sons, New Brunswick, N. J.

*Supplied by McNeil Laboratories, Inc., Philadelphia, Pa.

occurred occasionally, particularly with large doses. A reduction in dose usually corrected this feature. Drowsiness was not encountered with Meprospan, which is effective in smaller doses. True habituation was not seen.

Promazine.—Oversedation is the most frequently observed side effect. In two patients (4 and 7 years of age), grand mal seizures occurred for the first time following the administration of this compound. Several other children experienced increased hyperactivity which did not disappear with continued use but ceased after the drug was discontinued.

TABLE 1

GROUP*	TYPE*	NUMBER	BEST RESPONSE TO: MEPROBAMATE (MILTOWN, MEPROSPAN)	ZOXAZOLAMINE (FLEXIN)	RESERPINE (RAU-SED)	PROMAZINE (SPARINE)	NO EFFECT
1. Cerebral palsy (spastic)	I-B	8	5	1		1	1
	I-C	7	4				3
	II-B	15	9	1	1	2	2
	II-C	12	8	1		2	1
	III-B	9	7	1			1
	III-C	11	7			1	3
	IV-D	41	19	2	3	6	11
2. Cerebral palsy (athetoid)	II-B	3	2			1	
	III-C	4	3			1	
	IV-D	6	2			2	2
3. Behavior		51	24		9	12	6
4. Headache		12	7			2	3
5. Sleeplessness		17	8			6	3
6. Brain injury		14	4		3	1	6
		210	109	6	16	37	42
Total number of children receiving each drug			210	74	172	94	

*For definition, see "Subjects."

Tolerance occurred infrequently. A maculopapular rash appeared in one patient after the administration of 40 mg. per kilogram per day (tablet form). When this 7-year-old child was challenged some time later, a smaller dose produced a similar response. That large amounts of the drug may be given safely in some instances is demonstrated by its administration to a 9-year-old boy with cerebral palsy and marked psychosis. To prevent him from chewing his tongue and lips, he has been given large amounts of meprobamate daily (2.4 to 3.2 Gm. per day or almost 100 mg. per kilogram) (tablet form only effective) for a period of over 2 years; no serious side effects have been observed.

Reserpine.—During the first 2 to 4 weeks of therapy, most children had conjunctivitis, nasal congestion, or florid complexion. Some children went through a period of hyperexcitability before improvement was noticeable. Syncope occurred in only one patient.

Zoxazolamine.—Many children rejected the administration of zoxazolamine because of its unpleasant taste. Gastrointestinal upsets were common. Hypotonia, anorexia, or vomiting were observed in about half of the patients in our group. Following the administration of this agent to a child who

had roentgen and clinical evidence of a duodenal ulcer previously, there was a recurrence of gastrointestinal bleeding.[1]

DISCUSSION

Blind and double blind studies are the ideal methods for the evaluation of new drugs. Our efforts to obtain such data by this study have been unsuccessful for various reasons. In the absence of such data, comparative observations of the effects of more than one drug on each patient may provide serviceable information concerning the effects of agents within a given category.

Objective methods, such as the measurement of muscle tone, have been of limited value. One difficulty is that it is sometimes impossible to distinguish involuntary from voluntary muscle tone. Another is that, although certain drugs, such as zoxazolamine, can be shown to produce a decrease in tone, this change may not be associated with an increase in ability to use the muscles effectively.

Comparison of one drug with another does not, however, eliminate the possibility of a placebo effect. This effect can probably be reduced by administering an agent for several months; during this time the novelty of a new drug tends to disappear. Most parents usually recognize the effects which follow ingestion of a particular drug. When a number of parents report similar effects from a particular drug and request its continuance or renewal, the possibility of a placebo effect is reduced.

The management and treatment of a handicapped child are much more difficult when the patient is irritable, restless, apprehensive, and unable to sleep. Superficial psychotherapy, environmental changes, and mild sedatives may bring improvement for some, but many children require more comprehensive psychiatric attention. Pediatric patients with severe emotional disturbances should be under the supervision of a child psychiatrist or a Child Guidance Clinic, if these facilities are available and if the parents accept the need for such therapy. However, preference for psychotherapy is usually given to children whose response to therapy is most apt to be favorable, and it is frequently difficult to secure such therapy for children with severe motor handicaps. For these children, the use of tranquilizers and relaxants deserves consideration on the possibility that they may provide sufficient control of the child to permit him to be a candidate for such therapy.

Drug therapy with these agents is aimed at improving the behavior and well-being of selected patients and at facilitating their general management. Specific treatment of the primary condition tends to be more easily accomplished if feeding, dressing, sleeping, and behavior problems can be partially alleviated. The apparent improvement may also encourage the parents to increased efforts in the home care of the child. Planned activities for the child which previously seemed futile or impractical may become possible. These may include play activities, learning to do such things for himself as dressing, or the acceptance of the child in a nursery school. Further, the load of the parents may be lightened to such an extent that they may lead more adequate lives, both domestically and in relation to social activities. When the difficult secondary problems are relieved and

some improvement is seen, parents often take a more realistic view of their long-range problems.

SUMMARY

1. Handicapped and ill children in whom irritability, restlessness, apprehension, and sleeplessness are troublesome secondary problems, may benefit from adjunct therapy with tranquilizers and relaxants. Our experience over a four-year period with meprobamate, reserpine, promazine, and zoxazolamine is presented. In this series, such therapy of 210 children is evaluated.

2. Special mention is made of Meprospan, a new long-acting form of meprobamate in capsules, which is usually accepted and well tolerated by children, particularly if the contents of the capsule is mixed with food. Gradual release of the drug provides a more uniform and sustained action at reduced dosage. The possibility of side reactions is minimized.

3. Meprobamate (tablet and capsule) proved most useful and least toxic of the several drugs studied. Of the 210 children, 109 showed the greatest improvement on meprobamate, 59 showed a better response to one of the other compounds used. In 42 patients there was no improvement on any drug.

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THE EFFECTS OF KWASHIORKOR ON THE DEVELOPMENT OF THE BONES OF THE KNEE

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IN A previous communication by Jones and Dean[2] evidence was given of retardation in bone development, found by radiological examination of the hands of children admitted to the Medical Research Council's Unit in Kampala for the treatment of kwashiorkor. Assessments of maturity were made by using the *Radiographic Atlas of Skeletal Development of the Hand and Wrist*.[1] The retardation was judged against the development of a group of healthy African children of the same age.

The present paper shows the results of the similar examination of the knee in children suffering from kwashiorkor and in healthy children, with the help of the monograph recently produced by Pyle and Hoerr.[3] To gain some idea of the comparative value of knees and hands as indices of malnutrition, the hands of the children were also examined by the technique described in the previous paper.

The effect of malnutrition on the knee has not, it seems, previously been studied systematically.

The Healthy Children.—As in the other investigation, the healthy children were members of the families of the African staff of the Agricultural Research Station near Kampala for which the Medical Research Council's Unit provides a Child Welfare Clinic. They were all of the Ganda, the Bantu tribe that inhabits the district, and were all known to be thoroughly healthy. Most of them had attended the clinic regularly for the greater part of their lives. The fathers are well paid, food of all kinds is plentiful locally, and milk from the Research Station's own dairy herd is always available. The ages of the children were known exactly; they ranged from 8 to 38 months. There were 23 boys and 24 girls.

The Children Suffering From Kwashiorkor.—Although the grounds for the diagnosis of kwashiorkor were in general those previously described,[2] the children selected for the present investigation were all judged to be severely affected by the disease, and the group did not include mild or doubtful cases. All, therefore, were poorly grown and edematous. All had changes in the color and texture of the hair, and nearly all had marked skin changes. Their serum chemistry was characteristically altered. Their ages were less perfectly known than the ages of the healthy children but were believed to be accurate to within one month. There were 75 children in the group, 44 boys and 31 girls.

At times between 3 and 40 months after they had been discharged from

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hospital, 30 of the children returned and were x-rayed again, and the results of the repeated examinations have been included. The children had their ordinary home diets, except that for 2 weeks after their discharge they had a supplement of dried skimmed milk. It was very unlikely that the supplement had a considerable effect.

METHODS

X-Ray Technique.—Two pictures of the left knee of each child were taken, one anteroposterior and the other lateral. For the first, the child was supine on the table with the knee fully extended and the popliteal surface touching the film cassette. For the second, he was on his left side. The limb was flexed at the thigh and knee. The ankle was raised on a sandbag to bring the long axis of the tibia parallel to the film surface. The right leg was brought well forward and supported on another sandbag.

For the anteroposterior view, the x-ray tube was centered 1 cm. above the lower border of the femoral condyles. For the lateral view, the tube was centered over the medial condyle of the femur. The distance from the anode of the tube to the film was 91.5 cm. (36 inches). "Ilfex" nonscreen film was used in cardboard exposure holders. The current was 60 Ma. at 51 kv. and the time of exposure varied between 0.6 and 1.0 second.

Assessment of Films.—The large number of centers of ossification in the developing hand of the young child enables the stage of maturity to be judged largely by simple arithmetic. The qualitative appreciation of the refinements of shaping is of secondary importance. The knee, in contrast, contains few centers and, although some of the indices of maturity are quantitative (for instance, some are ratios obtained by measurement), most of them depend on the appreciation of small changes in bone profiles. It is fortunate that Pyle and Hoerr have described the changes, in great detail, as a smooth and continuous process that can be understood and followed easily by any one patient enough to reach familiarity with it. The tibial epiphysis, as it is seen in the anteroposterior view, provides a good example. It is at first an ovoid that becomes flattened on the lower (metaphysial) surface. In boys, at the age of 11 months, the upper (subarticular) surface is divided with almost perfect symmetry into flattened facets that make an obtuse angle, and the lateral and medial sides of the epiphysis are beginning to be pointed. At 18 months the lateral facet appears to be shorter than the medial, and the pointing of the sides of the epiphysis is less on the lateral side. At the same time, the lower surface has a convexity at its center (above a corresponding depression in the metaphysis). At 24 months the medial facet has a slight concavity. At 30 months the lateral facet also has a concavity. The point of the medial side has been lost and the side is squared; the convexity at the center of the lower surface is obviously the forerunner of the tibial tuberosity. While these changes are occurring, the surfaces with which the epiphysis will finally articulate or fuse are being molded to correspond, their alterations becoming obvious sometimes before, and sometimes after, those of the epiphysis itself. The nature of such a process makes any attempt at short cuts dangerous, and the procedure adopted was slightly more involved

than that recommended by Pyle and Hoerr. They advised that when the film of a child is to be studied, it should first be compared with the standard photograph for a child of the same age and sex. (The sex is important because the usual feminine precocity in bone development is well maintained in the knee.) Afterward, comparisons should be made with older and younger standards, as might be found to be necessary. We began in this way, but as each photograph was consulted, the age in months of each significant detail of the bones was written down. This method usually gave a clear indication of the "age" of the whole knee, but the final figure for age was decided by inspection of the list of ages rather than by the calculation of an average.

RESULTS

The results are expressed graphically in Figs. 1 and 2.

The Healthy Children.—The knees of the boys were nearly all at the stage of development usual in American boys of the same age, but the girls were mostly a little in advance of their American counterparts. The number of children was, however, too small for a proper statistical analysis of the difference, and the analysis must await the collection of a larger series that can be safely used as the basis for African standards.

The hands showed the advance over the American standards that was found previously.

The Children With Kwashiorkor.—There was retardation in the development of both boys and girls. It is demonstrated plainly in Figs. 1 and 2 that there is almost no overlapping between the healthy and the malnourished, and no statistical treatment is necessary to confirm the retardation.

In almost every child the knee was apparently more retarded than the hand.

The bones of the children with kwashiorkor, in comparison with those of the healthy children, were smaller, less well calcified, and had much less trabecular pattern. They also showed several abnormalities which were not present in the healthy children: (a) The cortex of the shafts of the femur and tibia was often very thin or almost invisible (in 95 per cent of the boys and 84 per cent of the girls). (b) The zones of provisional calcification in the metaphyses of the femur and tibia could not be clearly seen (in 95 per cent of the boys and 97 per cent of the girls). (c) The concave profiles of the lower part of the femoral shaft and the upper part of the tibial shaft were interrupted by slight but distinct swellings that were seen best in the anteroposterior view, suggesting fusiform distortion of the shafts (in 57 per cent of both boys and girls). (d) There were dense white lines at the ends of the femoral and tibial metaphyses (in 97 per cent of the boys and 77 per cent of the girls). (e) There was irregularity of the calcification of the edges of the femoral and tibial epiphyses (in 82 per cent of the boys and 77 per cent of the girls).

Transverse lines of the kind usually known as Harris's lines[2] were present on the femur or tibia in 84 per cent of the boys with kwashiorkor and in 74 per cent of the girls. Only 22 per cent of the healthy boys and 10 per cent of the healthy girls showed such lines.

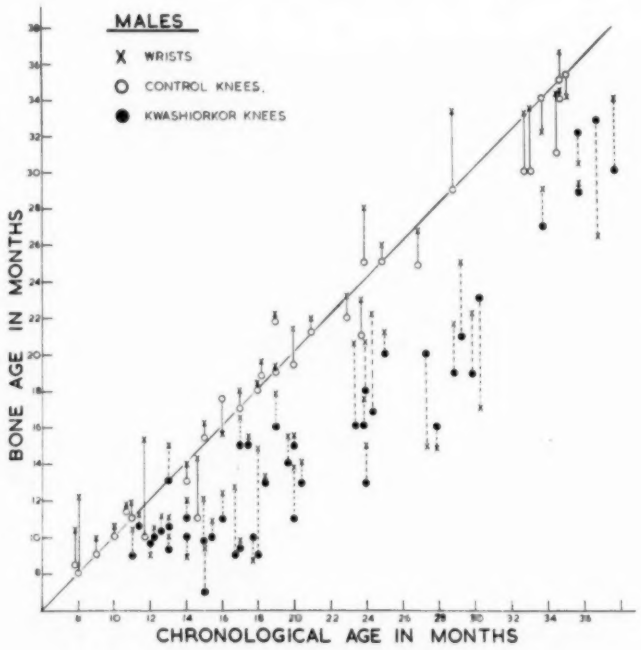

Fig. 1.

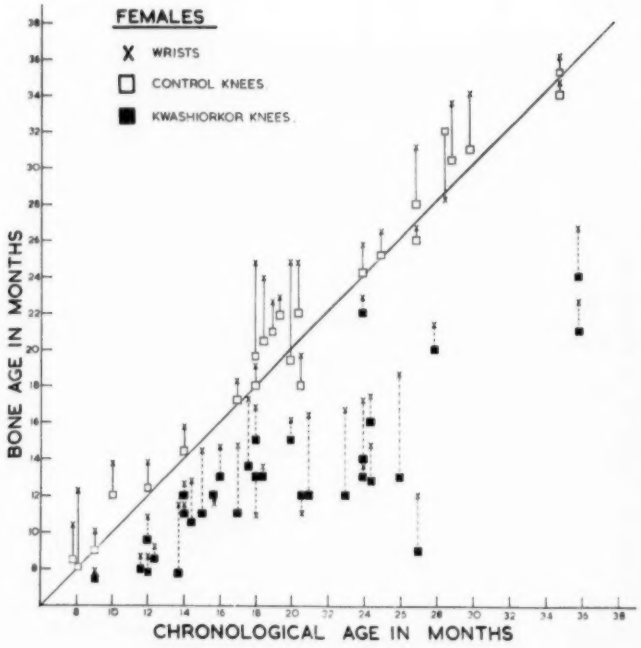

Fig. 2.

Figs. 1 and 2.—Diagrams illustrating the retardation of development found in kwashiorkor. The "bone age" (the age at which a healthy American child would attain the state of development found) is plotted against the actual age for boys (Fig. 1) and girls (Fig. 2).

Figs. 3 and 4 illustrate the kind of change that was usual. Both of the children whose knee bones are portrayed were of the same chronological age which was 19 months. The bones of the healthy child corresponded to the age of 22 months by the American standard, and those of the child with kwashiorkor to the age of 10 months. The figures show the abnormalities referred to in *a*, *b*, and *c* above. They also show, incidentally, the qualitative nature of the process of assessment. The disseminated calcification at the end of the femoral epiphysis of the healthy child is the only indicator of increased age that is added in the mathematical sense.

The advance in development found in the children who were x-rayed at follow-up examination is shown in Table I.

TABLE I. RESULTS OF FOLLOW-UP EXAMINATIONS
(All Ages in Months)

CHILD NUMBER	SEX	AT FIRST EXAMINATION			AT LATER EXAMINATION		
		CHRON. AGE	B.A.* WRIST	B.A.* KNEE	PERIOD†	ADVANCE WRIST	ADVANCE KNEE
1	M	6	3	3	10	6	6
2	F	12	8	8	6	2	2
3	F	12	9	8	6	2	2
4	M	13	10	9	11	7	7
5	M	13	15	13	10	13	5
6	M	14	12	11	15	8	7
7	F	14	12	12	3	1	0
8	M	15	11	10	12	5	6
9	M	15	10	7	12	6	6
10	M	17	10	6	7	2	3
					17	12	11
					25	18	17
11	M	17	15	15	23	3	6
12	F	17	17	11	7	6	2
13	F	18	22	13	12	5	6
14	M	20	15	14	27	15	16
15	M	20	15	13	17	14	14
					30	24	23
16	F	23	16	11	10	3	1
17	F	24	14	13	4	2	1
18	M	24	21	18	3	0	0
19	M	24	24	16	13	15	8
					17	22	12
20	M	24	22	17	13	12	13
21	M	24	15	13	34	18	19
22	M	24	18	16	9	9	2
					15	14	10
					26	32	22
					35	42	29
					40	48	32
23	M	25	21	20	6	7	8
24	F	26	18	13	7	2	1
25	F	27	12	9	3	0	0
26	M	28	18	20	9	4	3
					19	11	8
					34	24	22
27	M	29	25	21	4	3	2
28	M	29	22	19	13	12	15
					20	16	17
29	M	34	29	27	8	5	6
30	M	36	29	29	15	7	5

*Age of development by the American standards.
†Period in months from first examination.

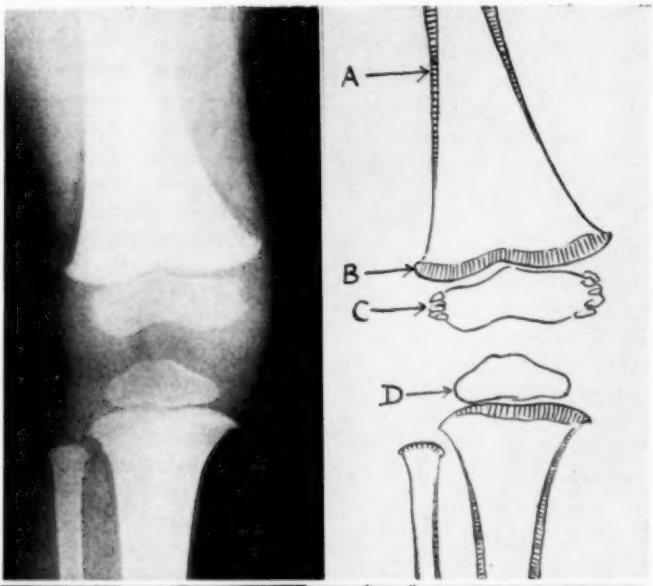

Fig. 3.

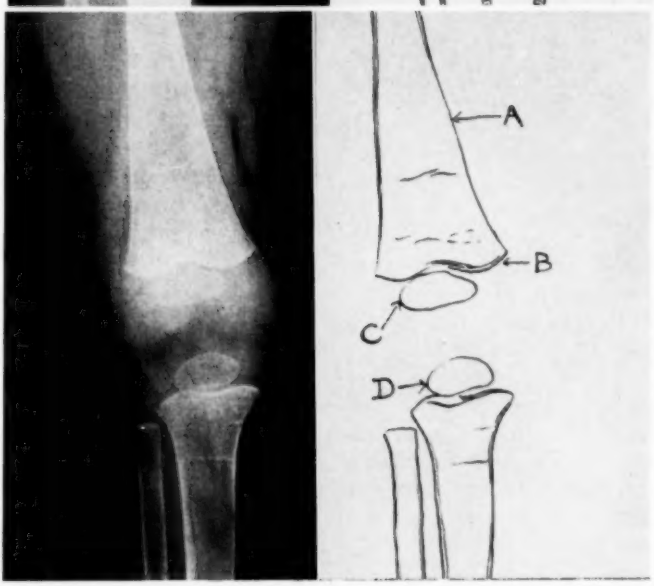

Fig. 4.

Figs. 3 and 4.—Photographs and tracings of radiographs of the knee of a healthy African (Fig. 3) and a child with kwashiorkor (Fig. 4). Both children were 19 months old. By the American standard, the bone age of the healthy child was 22 months, and that of the child with kwashiorkor 10 months. The arrows indicate: *A*, Good cortical outline in the healthy child; lack of outline, and fusiform distortion, in the ill child. *B*, Thick zone of provisional calcification; and its absence. *C*, Disseminated calcification; and its absence. *D*, A broad, well-shaped tibial epiphysis; and a small rounded one.

DISCUSSION

There was no doubt that in the children with kwashiorkor the development of the knees was greatly retarded. The greater degree to which the knees were affected in comparison with the hands may, however, be illusory. It seems that for healthy African children of this age group the development of the knee is very close to the American standard, whereas the development of the hand is in advance of that standard. An example may indicate the effect of this difference. There was a boy with kwashiorkor whose chronological age was 24 months. His knee had the development of an American boy of 18 months, and his hand that of an American boy of 21 months. The knee and the hand were therefore 6 months and 3 months, respectively, behind the American standard. The knee was also 6 months behind that of the healthy African child, but the hand was 3 months *plus* the extra 2 months which represents approximately the African advance. It is not possible at the moment to decide firmly whether the knee or the hand is the better index of malnutrition. Both parts seem to be severely affected, and it may be unwise to claim too much for the knee. There is, however, some additional evidence that favors the knee. In the paper[2] on the hand, it was shown by the calculations of coefficients of variation that the correlation of percentage reduction in bone age was greater with subischial height (that is, for all practical purposes, with the length of the long bones of the leg) than with stature. Similar calculations for the knee data show strongly positive correlations of the bone age with both subischial height and stature. The regression equation for the knee against stature is $X = 90.50 + 0.26 (y - 69.04)$, which gives a line almost exactly coinciding with that drawn for bone age of the hand against subischial height. However, the equation for the knee against subischial height, $X = 91.67 + 0.39 (y - 69.04)$, gives a line of considerably steeper slope. It is logical to expect the development of the knee joint to run parallel to the growth in length of the leg bones, but the calculations offer something that is less obvious: that in a series of cases of kwashiorkor, examination of the knee can replace measurements of height or subischial length when an index of growth failure is needed, and may be slightly more satisfactory, for that purpose, than examination of the hand.

The data in Table I show that in the majority of the children who were re-examined the advance of both knee and hand was less than was to be expected in the time which elapsed between examinations, and in nearly every case the knee advanced more slowly than the hand. Development must, to some extent at least, be determined by activity and the child suffering severely from kwashiorkor is usually immobilized to a remarkable degree. He may have walked well at the normal age, but subsequently have given up walking altogether for some months before admission to a hospital. After he is well on the way to recovery, he will start to walk again, but he will not walk sturdily for a long while. It is possible that manual dexterity, and with that dexterity the development of the bone of the hand, improves at a faster rate. This is guesswork that could be

reduced to fact only if the recovery of function in the upper and lower limbs were accurately measured.

None of the abnormalities found in the knees of the children with kwashiorkor can be considered to be alone diagnostic of the disease. For obvious examples, retardation of development is usual in rickets, an appearance suggesting decalcification is common after the long disuse of a limb, and weight-bearing bones that are decalcified may show a fusiform distortion. Nevertheless, the abnormalities taken together make up a striking picture that has not been described, so far as we are aware, in any other pathological condition. The knees, like the hands, were retarded much more than could be accounted for by the known length of the period of ill health, and there seems to be little doubt that their bones indicated with fair accuracy the true time of onset of malnutrition of a degree sufficient to arrest or delay development. In one respect the knee bones seemed to be superior as indices to those of the hand and wrist: they showed more of the transverse lines believed to indicate disturbed growth. The lines are, however, without any specific meaning, and the frequency of their appearance in children with kwashiorkor might indicate nothing more than a general tendency of such children to have succumbed easily to minor illness.

In a recent paper on children seen in a nutrition clinic in Alabama,[4] an account was given of the finding of minor anomalies of ossification. More of these anomalies were found in children in whom "nutrition had failed" than in children who showed "neither past nor present evidence of nutritional deficiencies." The children were from 5 to 14 years of age. Their anomalies were mostly details that we have observed but considered to be little more than extremes of "normal" appearances. For instance, we have noticed apparent notching at the distal ends of proximal phalanges but regarded it as being more likely to be due to a minor error of technique than to a fault in bone development. We thought it advisable, however, to reexamine all the x-ray films of the hand that we had available for children between the ages of 6 months and 4 years. There were equal numbers of children who were x-rayed when they were admitted for the treatment of kwashiorkor and children who were believed to be healthy. The most common of the anomalies that we found were pseudoepiphyses at the distal end of the first metacarpal bone and at the base of the second metacarpal bone, but they were present in almost the same number of children in each group. The incidence of the other anomalies was negligible. It appears, therefore, that the presence or absence of the anomalies cannot be related to kwashiorkor as we see that disease. However, it should perhaps be emphasized that the children examined by Snodgrasse and associates[4] were all older than our children and most of them were believed to be affected by vitamin deficiencies.

SUMMARY

1. Radiographs of the knees of African children admitted for treatment of kwashiorkor were compared with those of healthy children of the same age.

2. In the children with kwashiorkor there was the general appearance of

poor calcification. Also, zones of provisional calcification could not be clearly seen, the shafts of the femur and tibia were fusiform, the femoral and tibial metaphyses had dense lines at their ends, and the epiphyses were irregularly calcified.

3. Transverse lines, indicating past disturbances of growth, were much more frequent in the femur and tibia of the children with kwashiorkor than in the healthy children.

4. The hands of the same children were also x-rayed. Comparisons suggested, but did not conclusively prove, that the knee may be a more accurate indicator than the hand of the retardation of bone development associated with kwashiorkor.

5. The hands of the children with kwashiorkor did not show the minor anomalies that have been described in older children with nutritive failure.

We were fortunate in having Dr. W. W. Greulich with us in Kampala when we were preparing this paper, and we are very grateful to him for his advice and help. It is also a pleasure to thank Dr. Idell Pyle for her encouragement. Neither Dr. Greulich nor Dr. Pyle is responsible, however, for any mistakes we have made in reading our films, or for any unwise opinions we have expressed. In addition, we wish to express our gratitude to Dr. E. Berthet, the Director-General of the Children's Centre, Paris, and to Dr. M. Gaud, in charge of the Centre's African Affairs.

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HYPOPHOSPHATEMIC RICKETS DUE TO GLOMERULAR AND TUBULAR RENAL INSUFFICIENCY

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RICKETS is a syndrome caused by disturbances in the deposition of inorganic materials in the cartilage and in the bone which, according to the latest classifications,[1, 2] may be due to: (1) disturbances in absorption of calcium and phosphorus (vitamin D and/or dietary lack, diarrhea, steatorrhea, absence of bile and pancreatic juice); (2) renal insufficiency; (3) hyperparathyroidism, which etiology, although questioned, has been verified in the cases of Vogt,[3] Anspach and Clifton,[4] and Wood and associates[5]; (4) disturbance in balance of matrix production and/or destruction and deposition of inorganic elements ("physiological osteoid or rickets," healing scurvy, healing osteitis fibrosa); and (5) hereditary enzymatic defect interfering with local calcification (hypophosphatasia).

In rickets caused by renal insufficiency, according to Dent,[6] we differentiate glomerular rickets from renal tubular rickets and, in the latter, the types promoted by: (1) insufficient tubular reabsorption of phosphorus (hypophosphatemic or vitamin D-resistant rickets); (2) insufficient tubular reabsorption of phosphorus, amino acids, and glucose (Fanconi's syndrome); and (3) insufficient tubular reabsorption of bicarbonate and phosphorus with or without defective ammonia formation (hyperchloremic renal acidosis or Butler-Albright syndrome). Albright and Reifenstein[7] and Follis[1] point out that idiopathic hypercalciuria may also cause rickets or osteomalacia.

A case is reported here of a boy affected with rickets who has both glomerular and tubular renal insufficiency, of a type of salt-losing and potassium-losing syndrome. To our knowledge there are no previous references to this in the medical literature.

CASE REPORT

J. M. B., 12 years of age (Fig. 1), was taken to the Orthopaedic Department in September, 1955, because of symmetrical fractures of both tibiae. His height (92 cm.) and weight (14.150 Kg.) corresponded to that of a boy 3 years of age, and his mental age was 3.5 years.

He had been premature; born in the eighth month of pregnancy. His mother stated that when he was 40 days old he had had infantile diarrhea and at the ages of 4, 8, and 9 years respectively, he suffered from episodes of so-called meningitis. Up to the age of 10, he had frequent massive diarrhea with complete elimination of food. There was always thirst and polyuria. Previously he suffered several fractures of the right wrist.

The patient's parents are both young and there is no consanguinity. The

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mother suffers from pronounced deafness and her selerae are blue. One of the mother's sisters has a history of multiple fractures. One of the patient's brothers died when he was 9 months old from severe vomiting.

Finding of the physical examination were bulging forehead, moderate exophthalmos, ogival palate, normal teething.

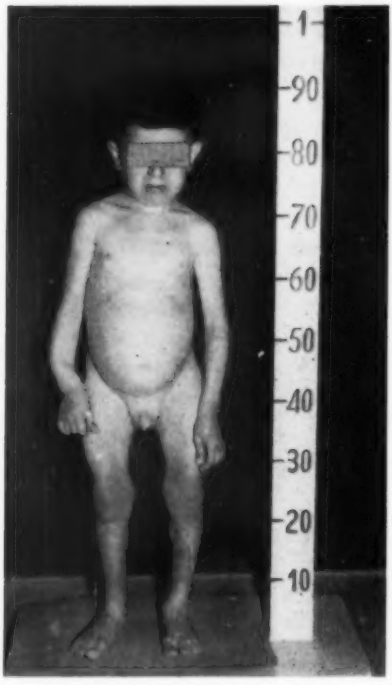

Fig. 1.—J. M. B., 12 years old.

Cardiac sounds were normal; pulse was 80, blood pressure, 80/55. He had a distended abdomen, small penis and testes, and bilateral inguinal herniation. The upper and lower limbs were very thin, the wrists broad. In the right forearm there was a pronounced deformity corresponding to a callus caused by a fracture. Bilateral coxa valga and genu varum were present.

Measurements were: span 95 cm., top of head to pubis 52 cm., pubis to ground 43 cm.

Radiological examination of the skeleton revealed an osteogenesis imperfecta and generalized rarefaction. Pronounced rickets was noted on both wrists and ankles (Fig. 2, *A* and *B*).

On both upper femoral metaphyses (Fig. 2, *C*) and on both tibiae and fibulae symmetrical Milkman pseudofractures were observed (Fig. 2, *B*). The bone age corresponded to that of a boy 6 years old.

Blood examinations were done by the following methods: the phenolic compounds with the xanthoprotein test of Becher[8] (normal up to 25 units); the protein according to Kagan[9] (normal 6.8 to 8 Gm. per 100 ml.); the calcium according to Clark and Collip[10] (normal 9 to 11 mg. per 100 ml.), the phosphorus according to Fiske and Subbarow[11] (normal 3.5 to 5.5 mg. per 100 ml.); the alkaline phosphatase according to Shinowara and associates[12] (normal 4 to 13 units per 100 ml.); the chloride according to Van Slyke[13] (normal 95 to 105 mEq./L.); the sodium according to Marenzi and Gerschman's[14] modification of Salit's method (normal 135 to 150 mEq./L.); the potassium according to Marenzi and Gerschman[15] (normal 3.5 to 5 mEq./L.); the alkali reserve according to Van Slyke and Cullen[16] (normal 25 to 30 mEq./L.).

The endogenous creatinine clearance was performed according to Taussky[17] (normal values corrected to the surface area of patient ranging between 95 to 130 ml. per minute).

In the urine, the phosphorus was tested according to Fiske and Subbarow[11] (normal 13 to 18 mg./Kg./24 hours); the calcium according to Waisman's[18] modification of Clark and Collip's method (normal 2 to 6 mg./Kg./24 hours); the sodium according to Butler and Tuthill[19]; the chloride according to Jeffrey's[20] modification of Volhard-Harvey's method; the aminic nitrogen according to Northrop[21] (normal 1 to 4 mg./Kg./24 hours) and with the bidimensional chromatography.[22]

In the stools, the total fats were tested according to Fowweather and Anderson[23] (normal ranging up to 25 Gm. per 100 Gm. of dried stools).

The serum and urinary chloride were determined simultaneously while the patient was submitted to a diet containing daily 45 mEq. of chloride, 45 mEq. of sodium, and 48 mEq. of potassium.

The analysis (Table I) disclosed the following: a red cell count of 4,300,000; leukocytes 7,800 with a normal differential count; hemoglobin 14.22 Gm. per 100 ml.; blood urea nitrogen 75 mg. per 100 ml.; calcium 9.2 mg. per 100 ml.; phosphorus 2; 2.5 mg. per 100 ml.; chloride 88.7; 83 mEq./L.; sodium 108 mEq./L.; potassium 1.66; 2.35 mEq./L; and alkali reserve 32; 39 mEq./L. Sedimentation rate was 40 mm. in one hour.

Endogenous phosphorus clearance was 30 ml./minute. Endogenous chloride clearance was 3.32 ml./minute.

Urine analysis revealed a specific gravity of 1.009, with no traces of protein or sugar. Urine pH was 7.4. The Addis count revealed 400,000 red cells, 300,000 leukocytes, and no casts. Phosphorus was 313.5 mg./24 hours; calcium 38 mg./24 hours; sodium 111 mEq./24 hours; chloride 113 mEq./24 hours; ammonia nitrogen 220 mg./24 hours; and amino acid nitrogen 177 mg./24 hours.

The intravenous phenolsulfonphthalein test revealed an excretion of 38 per cent in 60 minutes.

Stools.—Total fats were 12.77 Gm. per 100 Gm. of dried stools.

The pathological examination of a kidney segment obtained by puncture biopsy was limited to the medullar area (Fig. 3) which revealed a moderate selerosis and an abnormal dilatation of some tubules.

The diagnosis was hypophosphatemic rickets caused by glomerular and tubular renal insufficiency, associated with osteogenesis imperfecta.

TABLE I. LABORATORY DATA ON J. M. B.

	Oct. 25 to Dec. 9, 1955	Dec. 27, 1955, to March 27, 1956	March 28 to July 19, 1956	July 20 to Nov. 24, 1956	Nov. 25, 1956, to Feb. 23, 1957
Blood urea nitrogen (mg. per 100 ml.)	75	75	75	1	75
Serum phosphorus (mg. per 100 ml.)	2	2.95	4	2.6	3.48
Serum alakaline phosphatase (Shinowara-Jones units per 100 ml.)	12.3	11.5	10	12	9
Serum calcium (mg. per 100 ml.)	9.23	11.1	10.6	10	11
Plasma chloride (mEq./L.)	88.7	83	84.5	76.9	79.7
Serum sodium (mEq./L.)	108		112	120	128.6
Serum potassium (mEq./L.)	2.35	2.35	1.66	1.9	2.05
Radiological evolution (x)	+	++	++++	++	++++
Treatment calciferol units		50,000 to 100,000	150,000 to 200,000	50,000	50,000 to 100,000
Sodium chloride (Gm./day)		6	6	10	12
Citric acid (Gm./day)		5.6	5.6	5.6	5.6
Sodium citrate (Gm./day)		3.92	3.92	10.92	3.92
Potassium chloride (Gm./day)				7	

\+ Severe rickets.
++ Slight calcification.
+++ Moderate calcification.
++++ Normal.

Fig. 2A.

Fig. 2B.

Fig. 2.—Radiographs of wrists, ankles, and femorae before treatment.

A, Bone rarefaction, broadening of epiphyseal cartilages, fracture callus of radius and Milkman pseudofractures of both ulnae.

B, Bone rarefaction. Symmetrical Milkman pseudofractures of tibiae and fibulae. Broadening of epiphyseal cartilages.

On Dec. 10, 1955, treatment was initiated with daily 40 ml. Shohl's solution, which is equal to 5.6 Gm. citric acid and 3.92 Gm. sodium citrate. On December 27, a daily dose of 50,000 units of calciferol was added.

A normal protein, high carbohydrate diet was prescribed, containing 960 mg. calcium and 1452 mg. phosphorus.

On Jan. 5, 1956, the daily dose of calciferol was increased to 100,000 units, on January 27 to 150,000 units, and on February 9, to 200,000 units. From March 28, 1956, 6 Gm. sodium chloride in enteric-coated tablets was added daily.

made the exact control of the intake of sodium chloride difficult. From July 20, 1956, the daily dose of calciferol was lowered to 50,000 units, together with 40 ml. of Shohl's solution, 10 Gm. of sodium chloride, and 40 ml. of solution containing 7.7 Gm. sodium citrate and 7 Gm. potassium chloride.

A radiological control taken on Nov. 24, 1956, showed slight worsening, consisting of bone rarefaction and enlargement of the cartilages of the wrist. Laboratory examination revealed: blood urea nitrogen, 100 mg. per 100 ml.; phosphorus, 2.6 mg. per

Fig. 2C.—Generalized bone rarefaction. Symmetrical Milkman pseudofractures of both femorae.

On March 28, 1956, after 92 days of calciferol treatment, the serum phosphorus was 5 mg. per 100 ml. The radiological control taken after 122 days of treatment with calciferol revealed cured rickets (Fig. 4). The dose of calciferol was then reduced to 150,000 units. Although the intake of sodium chloride was increased to 10 Gm. daily, there was no increase of serum chloride or decrease of blood nonprotein nitrogen (Table I). It should be noted that the refusal of the mother to permit hospitalization of the patient

100 ml.; alkaline phosphatase, 12 Shinowara-Jones units per 100 ml.; chloride, 76.9 mEq./L.; sodium, 120 mEq./L.; and potassium 1.9 mEq./L. The daily dose of calciferol was increased to 100,000 units, the sodium chloride to 15 Gm., and the intake of the solution containing 7.7 Gm. sodium citrate and 7 Gm. potassium chloride was continued.

The roentgenograms of the wrists and tibiae obtained on Dec. 20, 1956, revealed considerable improvement with respect to previous ones. The

serum phosphorus was 5.56 mg. per 100 ml. The Sulkowitch test was negative. After suspending the calciferol for 5 days, the intake of this drug was continued, alternating 50,000 and 100,000 units.

On Feb. 23, 1957, the following humoral data were obtained: blood urea nitrogen, 75 mg. per 100 ml.; phosphorus, 3.5 mg. per 100 ml.; alkali phosphatase, 9 Shinowara-Jones units per 100 ml.; calcium, 11 mg. per 100 ml.; chloride, 79.9 mEq./L.; sodium, 128.6 mEq./L.; and potassium 2 mEq./L. The height was 94 cm. and the weight 13,800 Kg. His physical state and muscular strength had improved strikingly.

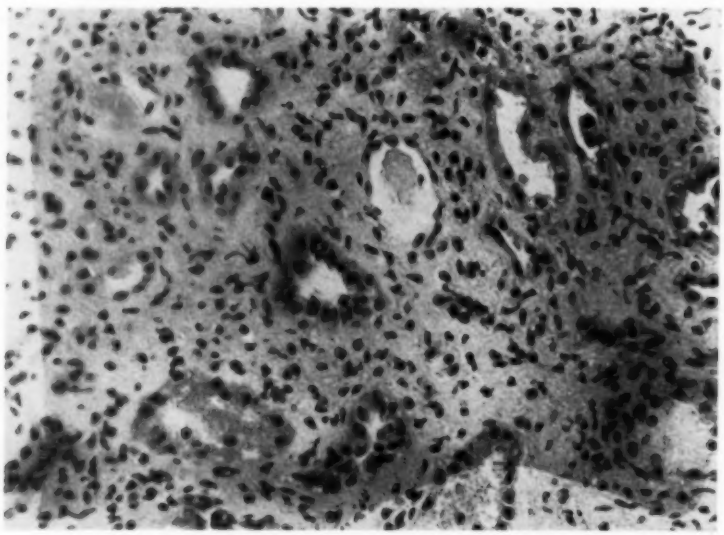

Fig. 3.—Section of the kidney biopsy. Note the interstitial sclerosis in medullar area.

The treatment with calciferol, sodium chloride, and potassium chloride was continued. Medication with chorionic gonadotrophins is planned in order to stimulate the secretion of androgens, to increase the osteoblastic activity, and to correct the osteogenesis imperfecta.

DISCUSSION

This case presents very intricate features (mental deficiency, dwarfism, rickets, osteogenesis imperfecta, and severe renal insufficiency), from which the osseous syndrome and its relation with the renal insufficiency will be considered.

The osseous syndrome was characterized by dwarfism, osteogenesis imperfecta, and rickets. The dwarfism may be attributed either to genetic causes, to the undernourishment provoked by diarrhea, or to the same causes that provoked rickets. The osteogenesis imperfecta, which was diagnosed by means of radiology and the relatively low serum alkaline phosphatase, was probably caused by genetic factors.

Rickets was verified by clinical and radiological examination of the skeleton. The symmetrical Milkman pseudofractures are attributed to rickets[24-27] and eventually to osteogenesis imperfecta.[28]

The laboratory data suggest that the rickets is due to low serum phosphorus

provoked by the high phosphorus clearance verified in this case of renal insufficiency. The normal serum calcium and the low calciuria rule out hyperparathyroidism, and the present absence of steatorrhea with normal average fats in stools discards the possibility of idiopathic steatorrhea.

The diagnosis of glomerular and tubular renal insufficiency is based on elevated blood urea nitrogen, positive xanthoprotein test, reduced creatinine clearance, and low excretion of phenolsulfonphthalein with hypochloremia with high endogenous chloride clearance, hyponatremia, hypokalemia, and hypophosphatemia with high phosphorus clearance. The pathological study of the kidney which was limited to a medullar area revealed solely an increased sclerosis and the dilatation of some tubules.

Owing to the lack of complete metabolic investigations in our patient, we were unable to discriminate correctly between a potassium-losing and a salt-losing nephritis. It should be pointed out, however, that potassium-losing nephritis is considered as a syndrome[29, 33] that may be caused indistinctly by primary aldosteronism, potassium depletion from gastrointestinal losses, and renal diseases (Fanconi syndrome, renal tubular acidosis, potassium-losing nephritis, and salt-losing nephritis), the most frequent pathological parenchymal renal disorders being glomerulonephritis, chronic pyelonephritis, and localized tubular insufficiency. Schwartz and Relman[34, 35] and Milne and co-workers[36] reported the potassium depletion nephropathy and its frequent complication with pyelonephritis.

The elevated alkaline reserve, which was also verified in our case, is attributed to the entrance of the hydrogen

Fig. 4.—Roentgenogram of the wrist after 92 days of treatment with calciferol. The epiphyseal cartilages are normalized and the bone has a normal density.

ions into the cells in substitution for potassium.[37, 39]

In some rare instances, as in the case of Earle and associates,[29] there were humoral manifestations of glomerular insufficiency associated with hypochloremia and eventually with hyponatremia, although not so significant as in our patient.

Referring to the salt-losing nephritis, the first clinical reference is due to Thorn and co-workers.[40] Besides the hypochloremia and hyponatremia, they verified that the patients suffered weakness, nausea, muscular cramps, and hypotension, symptoms which suggested the diagnosis of Addison's disease. The lack of response to desoxycorticosterone acetate was a guide to the correct diagnosis.

In most of the published cases there was acidosis. Only in one case of Murphy's[41] was high alkaline reserve found as in the present case.

The pathology of the so-called salt-losing nephritis, although not uniform as is the case of potassium-losing nephritis, consists most frequently of chronic pyelonephritis that eventually complicates the congenital defects of the kidney.

Concerning the lack of significant clinical symptoms, Murphy and associates[41] and Erieson and Svanborg[42] pointed out that in salt-losing nephritis the clinical manifestation eventually may not be pronounced. Black and Milne[38] stated that in potassium depletion the extracellular alkalosis prevents the muscular weakness. This may justify the absence of any significant symptoms related either with salt-losing or with potassium-losing nephritis in our patient.

Referring to the low serum phosphorus, which in J. M. B. elicited the rickets, it is very frequently associated with potassium-losing nephritis or with potassium depletion.[29, 38, 43-47] Mahler and Stanbury[46] and Brooks and associates[47] found in their cases a high phosphorus clearance, and the former authors associate the hypophosphatemia with the metabolism of potassium. In most of the published cases of salt-losing nephritis, there was no hypophosphatemia, although Goldman and Bassett[48] verified that the tubular reabsorption of phosphorus was reduced in the advanced stages of renal glomerular insufficiency.

It is noteworthy that in the published etiology of salt-losing nephritis, there are no references to osteomalacia. Erieson and Svanborg[42] described bone rarefaction in a patient, but the corresponding humoral and pathological data are not specified.

It should be emphasized that an increase of serum phosphorus and the consecutive cure of rickets were obtained with high doses of calciferol.

SUMMARY

A case is described of a 12-year-old boy who suffered mental retardment, dwarfism, osteogenesis imperfecta, rickets with Milkman pseudofractures, and glomerular and tubular renal insufficiency, of which the principal symptoms were high blood urea nitrogen, diminished creatinine clearance, elevated endogenous phosphorus and chloride clearances, hypophosphatemia, hypochloremia, hiponatremia, and hypokalemia. The eventuality that this nephropathy may be considered as a salt-losing or a potassium-losing syndrome is discussed.

Although the prognosis of the renal disease is discouraging, the rickets was cured in this case with high doses of calciferol.

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The "Rural" G.P. a Century Ago

"Pour suffire aux besoins de sa rude pratique,
Il faut qu'il soit doué d'un zèle hippocratique,
Qu'il soit en même temps médecin, accoucheur,
Dentiste, pharmacien, adroit opérateur.
N'ayant d'autre désir que celui de bien faire
Que de fois il n'a su recevoir son salaire!
Pour toute alternative, il doit, pour son prochain,
Succomber de fatigue on bien mourir de faim."

From Verses by Dr. A. Corlieu in
L'UNION MEDICALE, July 27, 1858

HANDLING PARENTAL PRESSURE FOR T AND A

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THE physician is subjected to many pressures by the parents of his patients. Typical is the insistence that he "do something to make the child eat." He can usually anticipate this pressure in mothers who seem anxious about their child's weight at each routine office visit. He usually copes with it by reassurance and by educating the parents about the normal individual variations in appetite. If he succumbs to the parental urging and prescribes a "tonic," he has not subjected his patient to any great stress.

Similar in many ways is the parental pressure for tonsillectomies. The pediatrician learns to anticipate it in mothers who ask anxiously at each visit, "How are his tonsils, Doctor?" Here, too, he tries to cope with parental pressure by reassurance and education. But how much more insistent the pressure for a tonsillectomy can become, and how different is the result if the pediatrician succumbs to it. Not only may his patient have an unnecessary operation with its attendant risks, but also, despite present knowledge and efforts at preparation of children for surgery, the patient will still endure a traumatic experience in undergoing surgery. Preparation for surgery, essential though it is, can only help a child cope with a trauma, it cannot eliminate the trauma.

Debate still continues about how often a T and A is necessary. Dr. Bakwin[1] has recently pointed out that there is as yet no controlled study to verify its efficacy and has wondered if, in the main, the procedure is ever indicated. The question of the indications for a T and A is beyond the scope of this paper. But it was thinking about this question that stimulated my interest in the parents' attitudes toward surgery.

As each physician tries to decide when to recommend the operation and how to evaluate its benefits, he finds many difficulties. I felt one complicating factor was the parents of my patients. In assessing the indications for surgery, I had to rely upon their histories; in evaluating postoperative results, I had to rely upon their observations. In the case of parents who pressed me for surgery, I wondered if their desire for the operation did not distort their reports. The more I thought about parental pressure and came to understand it, the better I felt I could deal with it. And what was particularly surprising, the number of my referrals for surgery decreased markedly.

My experience substantiates a point made by Dr. Bakwin,[1] namely, that

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parental pressure is one of the main instigators of surgery. Control of this factor not only might eliminate some unnecessary operations but also would allow more accurate assessment of the indications for and results of surgery.

What are the sources of parental pressure for tonsillectomies, and how can this pressure best be managed? I believe there are two sources: first, common misconceptions about tonsils and tonsillectomies that can be combated by education; and, second, parental feelings, some of which the pediatrician can manage.

The two misconceptions I found most common were, first, that the tonsils' only function is to be removed surgically; and, second, that any respiratory illness is a tonsillitis. Let me cite an example of each of these.

Recently, I saw a 6-month-old infant with pharyngitis which I explained to the family as a "throat infection." The father immediately wanted to know if now was the proper time to have the tonsils removed. When this first question is asked, I believe it is wise to explain some specific objective facts about the tonsils. In the long run, it actually saves time in eliminating endless questions at later visits. What the parents are told in answer to this first question will vary from man to man. However, it would seem important to make sure that the parents understand that the tonsils have a purpose, that the child may survive very nicely even if the tonsils never have to be removed, and that he may very well have attacks of tonsillitis and never require a tonsillectomy.

I used to battle the idea that any upper respiratory illness was a tonsillitis by being careful not to mention the tonsils unless the infection was primarily restricted to the tonsils. I changed my tactics when one family, whom I had very carefully handled in this fashion, insisted that their son had had four attacks of tonsillitis that winter. The record actually read: "nasopharyngitis; nasopharyngitis; minimal cervical adenitis; coryza." I now specifically say with such infections that either the tonsils are not involved or else their involvement is just part of a general throat inflammation. Apparently parents cannot be trusted to know that every respiratory illness is not a tonsillitis; in view of the universal strength of the misconception, this must be said to the parents specifically and repeatedly.

Every pediatrician is familiar with these misconceptions, would probably categorize them differently, and be able to offer many more examples. The only point I want to stress is that the time to do the educating is when the first question about the tonsils is heard. This is true even if, or perhaps most especially if, the question seems such an innocent one, as "And how are his tonsils, Doctor?" or such an illogical one as asking about a T and A with the baby's first cold. This is the time when the parents will be able to listen and understand, and they may not be able to understand later on. By then, they may already be feeling guilty that they have neglected their child by not having this common procedure done—in other words, his infections are their fault; his suffering is their responsibility. Once this reaction has taken place, education may be of no avail because the source of the pressure for the operation has moved from the parents' ignorance to their feelings. When

the parents' feelings are foremost as the source of the pressure, parents just do not accept the education; its acceptance is blocked by their feelings. The situation is not unlike treating a severely secondarily infected eczema. Local therapy for the eczema will be ineffective until the infection has been treated and eradicated. Until then, the infection will, in effect, block any other local therapy, no matter how sound and logical it may be.

This obviously leads to the second source of pressure, the parents' feelings and to one feeling in particular—guilt. How can the guilty parent be recognized? Often it is very easy. For example, some mothers frankly verbalize the feeling by blaming themselves for leaving their child in a draught. It is relatively easy to help the more mature and stable of these mothers by understanding their feeling and sympathizing with them and then explaining the reality.

Other guilty parents are not so easy to recognize, and therefore not so easy to help. These are the parents who are not fully aware of their guilt. They will often scold the child for being outside without his coat or rubbers or blame the school for not making him wear his raincoat home. When a mother blames someone else for something which most mothers would express or accept as the mother's responsibility, it would be reasonable to assume that this mother feels so guilty that she has to "put the blame" on another. If the child or the school is defended, it will only distress the mother. She is likely to feel that this is a subtle accusation; if the child or the school is not guilty, she is. This type of mother must be helped, tactfully and directly, to become more aware of her feeling of guilt. Sometimes all it takes is a simple "I guess it's hard for all mothers not to feel it's their fault every time their child is sick." When an affirmative answer is received to such a statement, the opportunity to understand the feeling and to sympathize is presented, thus removing the block to any explanation of the reality.

What other feelings of parents can lead to pressure for a T and A? I would mention one other, namely, angry frustration. This is often seen when a parent comes to the physician's office and asks for an evaluation for a T and A. The list of symptoms seems to be presented as a series of accusations against the child; he is constantly sick, constantly irritable, doesn't eat, doesn't sleep, and so forth.

It is hard to know why parents become so upset that they are eager to submit their child to a surgical procedure. However, if they can be helped to tell the full story, the situation becomes a little clearer. First of all the parents are tired—tired from the nights of nursing their child through the uncomfortable respiratory infection, and tired from the endless daytime humoring of the child, who is not quite well enough to be outside, not quite sick enough to be in bed. And what has been their reward for this great expenditure of patience and energy? Instead of being grateful for all his parents' sacrifices, the child seems to respond with more illnesses and more demands.

Someone must be to blame for such a frustrating situation. Often, it is felt that the parents have first blamed themselves, have become guilty, and then have started blaming the child. Regardless, they want the situation ended and a T and A must be the way.

The pediatrician who thinks of disagreeing can easily feel that this disagreement may make him the next recipient of the wrath he has sensed.

What to do? Handling this feeling without acquiescing is often difficult. I think it is helpful to let parents know that you appreciate how difficult the situation is. Tell them you realize how many sleepless nights and frustrating convalescent days they have spent and that you would be surprised if they had not lost their patience or had not become angry at the situation, the child, and themselves. Even better than telling them that you understand these things is getting them to talk about them: the frustration and, if possible, the anger.

Still even more effective is anticipating this situation, that is, judging which parents are losing their patience and discussing it with them. Sometimes parents can be helped to talk out their anger and frustration before it erupts in an irresistible pressure for surgery. Often, a request for surgery can be anticipated and discussed with the parents before the pressure of their feelings will prevent their listening to any realistic advice.

It seems worth mentioning a third instance when parents' feelings may be the force behind the pressure for surgery. This occurs when the child's main complaint has nothing at all to do with the tonsils, but rather may be bed-wetting, a refusal to eat, or almost anything else that has baffled and frustrated the parents. Sometimes parents will state frankly the nontonsillar reasons for the request for surgery but, unfortunately, this is all too rare. Usually, these other reasons are discovered only after being a little incredulous about the original reasons presented and letting the parents talk for a while about why they want the child to have surgery. What is going on here is that the parent-child relationship has deteriorated in one particular area, and the child has developed a symptom or problem that does not respond to any of the parents' efforts. Almost unbeknown to themselves, the parents switch the area of conflict from one in which they have been constantly unsuccessful and frustrated to one in which they feel they can be successfully active, namely, securing a T and A to combat respiratory infections.

An example might be helpful here. A 7-year-old girl was brought to my office for a routine checkup. When I asked about any problems, the mother replied that the child "just did not eat." When I asked how long this symptom had been present, I was assured that it had been there uninterrupted since birth. Later, in taking the history, I was told that a T and A had been performed three years previously. The indications for the procedure had been many, all subjective and unrelated to the tonsils, but foremost among them was the child's refusal to eat. When I inquired about the success of the operation, I was assured that it was complete and that the child's eating had been vastly and permanently improved. When I referred back at this point to the presenting problem, the mother was confused. She was so certain that the operation had successfully cured the eating problem that the only solution to her dilemma was to surrender the current eating problem. It is hardly necessary to add that the child's weight curve was a normal one with no fluctuations before or after surgery.

This example is presented not just to show how an eating problem can be the source of parental pressure for a T and A, but also to enable me to present one other thought. Very often reports are heard of the most unusual symptoms being "cured" by a T and A, just as this little girl's eating problem had, in the eyes of her parents, been cured by surgery. Whenever parents' feelings become the instigating source for a surgical procedure, it is these feelings that may be "cured" by the operation, with the ensuing, almost miraculous results. Something in the parents has been cured, but the child remains unchanged.

This can also come about in other ways. For example, if a child feels that the surgery is a threat or punishment for some behavior or complaint of his that is disturbing to his parents, he will suppress this behavior or complaint, feeling that if it persists he may incur even greater consequences.

SUMMARY

1. There are at least two sources of parental pressure for T and A: widespread misconceptions about the need for surgery; and parental feelings, such as guilt or frustrated anger.

2. Such feelings may represent the parents' response to repeated respiratory illness in the child or to difficulties in their relationship with the child that are unrelated to his physical health.

3. Educational efforts to combat misconceptions about surgery can be successful if done early. They must begin when the parents ask their first questions about the tonsils, respiratory infections, or T and A.

4. Two points are important and merit repetition. Once the parents' feelings have also become a source of pressure, any understanding of educational efforts may be blocked until the feelings themselves have been dealt with. Furthermore, it is when the parents' feelings have become the motive for surgery that the amazing results of surgery are found that otherwise defy logical medical explanation.

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INTERSCORER AGREEMENT FOR THE GRAHAM BEHAVIOR TEST FOR NEONATES

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THIS study constitutes the first step in an investigation designed to ascertain to what extent the findings of Graham and associates[1] in their study of neonates, done at the Washington University School of Medicine, can be replicated by other workers in another environment. In particular, we are concerned here in whether other psychologists or professional personnel can train themselves to examine neonates with as high a level of interscorer agreement or reliability as that reported by Graham.

There were five different scales used in the St. Louis study: pain threshold, maturation scale, vision scale, irritability rating, and muscle-tension rating. The latter four were used in the present study. Work on pain threshold is now in progress. All of these scales have been used in connection with studies of anoxic infants.[2-4] Currently there is considerable interest in neonatal evaluation, hence, our experience to date with these scales may be of interest. A full description of the measures used is found in Graham and co-workers[1] and will not be repeated here.

The procedure used is as follows: (1) The authors familiarized themselves with the published description of the St. Louis measures.* (2) They examined three babies together consulting the monograph and each other freely. (3) Each examiner administered the procedures independently ten times, occasionally exchanging general comments. (4) A joint examination of infants began, and continued from March to June, 1958. After each item had been administered, the examiners went to different sides of the room and recorded their score or judgment of the response. When the entire examination was completed, they compared notes and scoring. The first large discrepancy between the examiners' ratings on the maturation scale occurred on the examination of the fifth neonate. On the immediately subsequent examinations, notes were compared after each response was recorded. Although there was no opportunity to change prior judgments, this allowed a closer look at the other person's bases of judgment. After several examinations were conducted in this manner, the examiners returned to the earlier method of completing the entire examination before comparing notes. In none of these periods did either examiner attempt to impose his interpretation on the other examiner. Good

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*They later obtained from the authors some supplemental information pertinent to the handling of data. Still later (about halfway through the study), the first author attended a workshop on the use of these procedures with Dr. Bettye Caldwell.

agreement under these conditions would indicate that we are dealing with behaviors that are reliably scorable under considerably less than optimal conditions.

The data reported here are for the infants examined jointly except for one 20-day-old child who had been delivered by cesarean section at 35 weeks. The babies were all clinic cases from one of the nurseries of the Providence Lying-In Hospital. They were all considered normal at the time of the examination to the extent that they were not in the nursery which handles all premature and problem babies. Data from 23 babies are reported here; however, there was a 1-day-old boy on whom we were unable to get a score for vision, and a 3-day-old boy to whom we did not administer the maturation scale. The distribution of examined babies by age and sex is shown in Table I.

TABLE I

DAY OF LIFE	SEX		
	MALE	FEMALE	TOTAL
1	2	2	4
2	3	3	6
3	4	3	7
4	2	2	4
5-7	2		2
Total	13	10	23

RESULTS AND DISCUSSION

Maturation Scale.—The maturation scale was the primary focus of our interest. It has a maximum score of 21 with half-point intervals. The actual range of scores obtained on these "normal" babies was from 8 to 20½ for one author, and from 7 to 21 for the other. The mean scores were 15.3 and 15.5 and the standard deviations 3.53 and 3.64, respectively. This provides a general picture of the similarity in the scoring. The actual interscorer agreement as shown by the Pearson coefficient of correlation is 0.84 as compared to 0.97 which Graham and associates found. There are several factors which may contribute to the somewhat lower correlation found here: (1) The examiners had less experience. (2) A certain amount of ambiguity results from the difficulty of recapturing from print all the criteria used by the test constructors for making a given judgment. (3) One examiner did not try to train the other to score in a certain way. (4) The fact that the 24 babies for whom the St. Louis group reported interscorer agreement included 5 traumatized babies might tend to raise their agreement since there is a tendency for curtailed distributions to produce lower coefficients of correlation. In any event, the agreement found in this study is satisfactorily high. Of all the items in the maturation scale, the one which gave the examiners the most difficulty, and the one which most often was at variance when there was a considerable disagreement between the judges, was the reaction to auditory stimuli. The criteria used to score the neonate as "listening" included decreased body movements and increased eye movements or head movements. It is more difficult to judge the occurrence of these responses than it is to judge the startling or blinking responses (which receive a lower score). It is our opinion that physiologic measures such as breathing rate would aid in the determination of a "listening" response.

Vision Scale.—The maximum score possible on the vision scale is 10. One author gave scores over the range from

0 to 10, the other from 2 to 10. The average scores were 4.95 and 5.05 and the standard deviations 3.03 and 2.74, respectively. The actual interscorer agreement as shown by the product moment correlation is 0.77. This compares with an r of 0.90 obtained by Graham and associates. The magnitude of the difference in interscorer agreement between the two studies, then, is nearly the same for the first two scales. As in the case of the item dealing with hearing on the maturation scale, we often did not feel confident of the judgments of vision. To date, however, we have no supplemental technique to suggest which might increase the reliability of this measure. The same reasons that were given for our coefficient of correlation being lower than that found by Graham and coworkers in the case of the maturation scale might be expected to hold here also. In the vision test, 4 of Graham's 21 subjects were traumatized babies. There is also the possibility that vision is easier to test in the babies born in the St. Louis Maternity Hospital where they do not use silver nitrate in the babies' eyes. Although the correlation is not quite as high for the vision scale as it is for the maturation scale, it still indicates an acceptable reliability of rating or agreement.

Irritability Rating.—Irritability had been rated by the St. Louis group along a continuum from 0 (normal, occasional cry to major stimuli) through 1 (fussy, occasional cry to minor stimuli) to 2 (irritable, frequent cry to minor stimuli). They then measured to the nearest 0.25 rating points (i.e., one-fourth of the way from 0 to 1 or from 1 to 2 on the line) to determine their agreement. We preferred to mark the line off into four categories and determine whether or not we had placed the child in the same category. Therefore, we did this as well as making the determinations in the way Graham and associates did. We are in agreement to about the same extent using either system—namely, perfect agreement in 43 per cent of the cases. There was considerable difference between the two examiners in counting the child as "fussy" if he seemed hungry or disturbed by major internal stimuli. One of us gave a more extreme rating than the other in 10 of the 23 cases, whereas the reverse occurred only two times.

This agreement may be better than it seems if we consider the fact that the St. Louis group only used this rating in terms of whether the baby was at zero or was above zero. If we examine the question of how well we agree on this type of placement, we both place the infant in the first of our four categories ("normal") or both place him outside of it ("fussy" or "irritable") in 61 per cent of the cases. Our first category is broader than the range for normality in the way Graham and co-workers measured their data. Our agreement as to whether the infant is or is not at zero by their criterion is 78 per cent perfect. There is no doubt that if one person took responsibility for setting the criteria and trained another person to make the same kind of judgment, a closer agreement could be reached. We should note that in ratings of this kind the smaller number and the curtailed range of babies seen by the examiners is probably a handicap. There is a tendency to try

to spread the judgments over the entire scale, but we were not examining babies who would be expected to be at the bottom of the scale. Such a rating has to take into account not only the behavior that occurs, but also the extent to which that behavior is judged normal for the stimuli causing it.

Tension Rating.—In the tension rating as in the irritability rating, we broke up the scale into discrete units. Here we used 5 units—one centering around zero and so scored, one each around +1 and −1, and one each around +2 and −2. We were in perfect agreement on placing the infant in a given one of the 5 categories in 65 per cent of the cases. However, if we measure the location of our judgments to see if they are within 0.25 score unit of each other, we find that we had perfect agreement in only 52 per cent of the cases as compared to the 79 per cent "perfect" agreement their 0.25 score unit. In either case we are in perfect agreement 70 per cent of the time.

As was true in the St. Louis study, we are in perfect agreement more often on the tension rating than we were on the irritability rating. However, if we take the score in relation to the cutting point of zero or not zero, we are not in as good agreement on tension as we were on irritability. Here it may be particularly important that we did not see any grossly abnormal babies. They would, in essence, have provided anchor points for our judgments. This view is further supported when one considers how we distributed our judgments. This distribution and a comparison of it with that obtained by the St. Louis group shows that we tended to place fewer neonates at zero and considerably more at the extremes despite the fact that we were not seeing traumatized babies. Table II shows the two distributions.

TABLE II. TENSION RATINGS

RATING*	0	0.25	0.5	0.75	1.0	1.25 AND OVER
Present study	41	9	11	13	19	7
St. Louis study	79	9	7.5	1	3	0.5

*Per cent of ratings at zero and various distances from it for two examiners.

achieved by the St. Louis group using this system. This is not as satisfactory a level of agreement as one would like.

It is again pertinent to see how well we agree on whether an infant is to be placed with the normal or not normal according to the St. Louis criteria. Here again their cutting point was zero versus not zero (i.e., above or below zero). Here it turns out not to matter whether we measure in terms of our 5 category scale or in terms of In the case of our ratings, the percentages are based on the ratings of both examiners, i.e., there are 46 ratings of the 23 neonates involved.

SUMMARY AND DISCUSSION

In summary, this study shows that it is possible for two persons with relatively little special training in the use of the Graham techniques to apply them in a reasonably consistent or reliable fashion. The maturation and vision scales seem to depend less

on extensive experience with neonates than do the irritability and tension ratings. However, the amount of additional experience needed to achieve good agreement, especially if the experience can include some stressed babies, would not seem to be great. Also, further codification of the procedures might help. Even the present level of agreement is fairly satisfactory for purposes of dichotomizing between "normals" and "not normals."

This would indicate that these measures are stable enough to allow the assumption that aspects of neonatal behavior are in fact being measured. This means that attention can be turned to other questions such as: (1) establishing norms for each day of life, and (2) finding whether a given baby tested on different days of his life will test in the same range. The latter question is very important. Are the behaviors which two people can measure reliably in a given test session stable from one session to another? Graham and associates have examined this question by getting test-retest agreement after 24 hours. They found acceptable correlations (from 0.62 to 0.69) but correlations lower than those found in their interscorer agreement study. This is to be expected since the average scores obtained by neonates typically increase with age. On the irritability and tension ratings, the test-retest agreement (done by one tester) was higher than the interscorer agreements (75 and 86 per cent perfect agreement compared to 68 and 79 per cent). In other words, irritability and tension ratings may vary more with the individual tester than do the other scales. The data presented here on the irritability rating suggest this conclusion. Systematic day-by-day testing of neonates during their hospital stay is planned as is the retesting of babies after 24 hours or more by the same and/or a different examiner. This latter procedure will give us some indication of whether irritability and tension are more stable aspects of the child's behavior (i.e., change less with age over the first 5 days of life) or whether there is merely more stability in the ratings of these aspects of behavior as given by a single examiner.

The stability of a baby's ratings or scores is particularly crucial in regard to the question of whether a child might, for example, on three successive days test normal, abnormal, normal (or in reverse order). This decision involves the establishment of cutting points in the distribution of scores on any scale so as to classify a child on one side of the cutting point as normal and on the other side as abnormal. Graham established such cutting points for the St. Louis sample. It is these cutting points which are referred to in the discussion of the irritability and tension ratings in terms of the use made of the data. Whether or not a baby was judged normal or not normal might be accidental (depending on which day he was tested) unless norms are available for each day of life based on the population of the hospital in which you are working. Norms based on a given hospital allow some control for the general practices (e.g., anesthesia procedures, etc.) of the hospital. The establishment of the interscorer agreement and the test-retest reliability of a laboratory test for the presence of a disorder is always the first step in

establishing its predictive value. One must then adopt tentative criteria for the classification of an abnormality, discovering which cut-off points serve to include the greatest number of correct diagnoses (clinically determined now, then clinically verified over a period of time). Work in these directions is proceeding, using a very slight modification of the Graham scale developed by one of us (J. F. R.).

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Was the difference due to climate?

Statistical Table Exhibiting the Mean Height of American Recruits.—The following, extracted from Surgeon General Thos. Lawson's report, exhibits the mean height of 1800 men taken as they were entered upon the recruit list filed in the Adjutant General's office. The results are given for 100 men from each State. No recruit under 5 ft. 5 in. is received.

STATE	SIX FEET AND OVER	GREATEST HEIGHT *Ft. In.*
Indiana	18	6.4¼
Kentucky	18	6.3¾
Ohio	15	6.3½
Tennessee	18	6.3
Maine	11	6.2
Vermont and New Hampshire	6	6.1
Massachusetts and Connecticut	5	6.3
North Carolina	24	6.3¾
Georgia	30	6.6½
South Carolina	15	6.4½
Alabama	17	6.4
Virginia	15	6.2
New York	4	6.1½
Pennsylvania	5	6.1
New Jersey and Delaware	6	6.1
Maryland	9	6.2
Illinois	17	6.3
Missouri	8	6.1½

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FULMINATING PURPURA WITH GANGRENE OF LOWER EXTREMITY NECESSITATING AMPUTATION

Case Report

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FULMINATING purpura (Schönlein-Henoch disease) is observed infrequently. The following case is reported to illustrate the manifestations of this syndrome and to document the occurrence of irreversible necrosis necessitating amputation.

CASE REPORT

A 3-year-old white girl was admitted to the Beth-El Hospital after one week of illness. The initial symptoms had been fever and lassitude of three days' duration. A diffuse erythematous rash developed one day after onset and persisted for three days. An ecchymotic area appeared over the left hip on the fifth day of ilness, one day after disappearance of the rash. On the sixth day, ecchymoses of the right hip and left thigh and painful swelling of the left ankle were noted. Within another twelve hours the entire left lower extremity became edematous. At this point the patient was hospitalized.

No medication of any kind had been taken during the six months prior to this illness. The remainder of the history was noncontributory.

On admission the patient was in mild shock, acutely and critically ill, afebrile, dehydrated, lethargic, and pale. Mild nasopharyngitis was present. A soft systolic murmur of functional type was heard at the lower end of the left sternal border. The heart was not enlarged and no thrill was palpable. Blood pressure was 110/60. The lungs were clear. Spleen and liver were not palpable. Neurological survey was normal. No unusual lymphadenopathy was present.

Ecchymotic areas were noted at the posterior and lateral aspects of both right and left hips. There was also swelling and generalized ecchymosis of the entire left lower extremity. This extremity was tender and the tissues were under increased tension. Slight ecchymoses of the elbows and face were also present.

Laboratory studies on admission were the following: hemoglobin 13.5 Gm.; white blood cells 23,200; differential smear of peripheral blood revealed 6 per cent myelocytes, 12 per cent metamyelocytes, 10 per cent stab cells, 50 per cent segmented polymorphonuclear leukocytes, 8 per cent eosinophils, 10 per cent lymphocytes, and 4 per cent monocytes, with toxic granulation of the leukocytes; platelets 200,000 per cubic millimeter; prothrombin time 35 per cent; bleeding time 3 minutes; coagulation time (capillary tube method) 5 minutes; clot retraction normal; sedimentation rate (Wintrobe) 14 mm. per hour; hematocrit 35 per cent; and urinalysis normal. Factor V deficiency of the blood was ruled out. Repeated blood cultures were negative. Culture of the nasopharynx revealed a mixture of organisms mainly staphylococci and *Neisseria catarrhalis*. Bone marrow aspiration revealed only a "toxic picture" with granulocyte/erythrocyte ratio 80:20. Liver function tests were normal. Coombs' test was negative. Spinal fluid was normal. Chest roentgenogram was normal.

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Course in Hospital.—The patient was treated with adequate amounts of vitamin K and ascorbic acid parenterally, intravenous fluids, intramuscular penicillin, and intramuscular ACTH 25 mg. every 6 hours. The course was characterized by absence of fever and gradual extension of the hemorrhagic areas. The subcutaneous ecchymosis rapidly spread to include bullous formations containing sterile, clear, straw-colored fluid; a hematoma developed in the left labium together with superficial ecchymosis of the adjacent skin of the abdomen; and the hemoglobin dropped to 8.8 Gm. with 2.1 million red blood cells. The patient was transfused with blood, and chlortetracycline was administered as a further prophylactic measure.

Fig. 1.—Gangrenous foot and lower part of leg. Necrotic area of knee healed completely. *A*, Early stage of gangrene; *B*, late stage of gangrene.

almost the entire right lower extremity. The patient had been placed on the abdomen because of the predominantly dorsal distribution of the necrotic areas. Within 12 hours a necrotic area 2 inches in diameter and circular in shape covered the left knee. Within 24 hours after admission the ecchymosis of the left lower extremity had progressed to vesiculation and

On the third hospital day fullness and tenderness in the left flank were discovered and interpreted as an intra-abdominal hematoma. Serial urinalyses failed to indicate any renal pathology. On the fifth hospital day a diffuse mild ecchymosis of the lateral aspect of the right thigh was noted. There was then rapid development of swelling of the entire right lower extremity plus

ecchymosis and a generalized cyanotic tinge of the right ankle. Despite the progressive deterioration in the lower extremities, there was continuous improvement in the patient's general condition.

After one week in the hospital, there was improvement of the proximal leg and thigh on the left with almost complete clearing of the involved area on the knee. Within two weeks the right lower extremity was entirely normal. After five weeks there was a definite line of demarcation of gangrene 2½ inches below the left knee. Throughout the entire course the pulsation of the femoral arteries had been palpable and roentgenograms of the gangrenous extremity revealed no evidence of osseous necrosis. Amputation below the left knee was subsequently performed (guillotine type) by Dr. Joseph Anton. The skin flaps were approximated by secondary closure and there was uneventful healing.

The amputated extremity was examined by the pathologist (Dr. David Spain) who reported the following: "Specimen reveals several small arteries with organizing thrombi in the lumen. The walls of the vessels reveal focal fibrinoid necrosis. Scattered throughout the walls of these vessels are acute inflammatory cells including eosinophilic leukocytes. These extend around the periphery of the vessel. The outer layers of the vessel walls are indistinct and merge into the surrounding tissue."

On the eighteenth day of illness desquamation was noted about the finger tips together with scaly desquamation of the skin of the lower abdomen. This process appeared identical with that seen following scarlet fever. Unfortunately, no definite decision as to the presence or absence of a preceding episode of scarlet fever could be made. During the fourth week of illness the dosage of ACTH was gradually diminished and discontinued.

This child subsequently was fitted with a prosthetic limb. She participates in a full program of physical activity and has made a good psychological adjustment.

DISCUSSION

Gairdner[1] divided the manifestations of this syndrome into three main groups: (1) skin lesions, (2) visceral lesions, and (3) joint lesions.

Osler[2] originally divided the skin lesions into four categories: (1) purpura, simple or with edema and bullae; (2) effusion as in ordinary urticaria or angioneurotic edema; (3) erythema, diffuse or localized with or without swelling; and (4) necrotic areas of skin. These necrotic areas are usually symmetrical and restricted to pressure points at the lower extremities, buttocks, and lower part of the back. Muldoon, Berg, and Kinnaird[3] reported that the areas of necrosis may be quite widespread and need not be limited as described by Osler. An exanthema consisting of crops of macules with either patchy or widespread distribution may be a feature of the syndrome. Purpura is not necessarily present.

The histology of the rash is described by Gairdner[1] as an "acute aseptic inflammatory reaction around the vessels of the corium, with frequently tissue eosinophilia. . . ." Wassilief is quoted by Gairdner as describing endothelial proliferation of vessels leading to obstruction and medial necrosis of arterioles.

Gastrointestinal symptoms and hemorrhage are common. Nephritis is also frequently a facet of the syndrome and is believed to be the same as the nephritis of Bright's disease.

Joint swelling and pain have been described. Although these symptoms

are referable to the joints, the pathological processes are periarticular.

Fulminating anaphylactoid purpura is believed to be etiologically related to bacterial hypersensitivity. Lewis[4] has reported a preceding upper respiratory infection in 50 per cent of the cases. In 24 per cent of the cases hemolytic streptococci were found on cultures of the nasopharynx. In a control series of upper respiratory infections similar cultures revealed hemolytic streptococci in only 7 per cent of the cases. In reported cases there was an average interval of 11 days between antecedent respiratory infection and Schönlein-Henoch syndrome (most cases 7 to 14 days and extremes of 3 to 35 days). Many features of anaphylactoid purpura are common to glomerulonephritis and rheumatism, which are also generally believed to be related to bacterial hypersensitivity. Cases following scarlet fever have been reported by Schick.[5]

Medal and Reynoso[6] state that the effectiveness of steroids and ACTH lacks uniformity and varies with the symptomatology. They have proved excellent for relief of abdominal pain, good for relief of joint symptoms, fair for cutaneous manifestations, and of no value for renal lesions.

SUMMARY

A case of fulminating anaphylactoid purpura has been reported. This case illustrates the appearance of an early erythematous macular rash followed by widespread areas of necrosis of the skin. All areas of necrosis subsequently healed with the exception of the left lower extremity below the knee. In this area the necrosis progressed to gangrene, necessitating amputation. Although ACTH and antibiotic therapy were undoubtedly instrumental in the preservation of the patient's life, they were ineffectual in preventing or reversing the gangrenous process in the left lower extremity.

Grateful acknowledgement for the help given in the management of this case is made to Dr. Béla Schick (Director of Pediatrics), Dr. Joseph Anton (Chief Attending in Surgery), and the late Dr. Samuel Feldman (Chief Attending in Peripheral Vascular Diseases), Beth-El Hospital, Brooklyn, N. Y.

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PHENYLKETONURIA: AN UNUSUAL CASE

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PHENYLKETONURIA (phenylpyruvica oligophrenia) was first described by a Norwegian biochemist, Følling,[1] in 1934. Much information regarding the physical characteristics of the disease has been compiled; however, there have been few cases reported of patients with normal or near normal intelligence.

Review articles by Wright,[2] Kretchmer and Etzwiler,[3] Paine,[4] and Knox and Hsia[5] have defined the syndrome as an enzymatic abnormality involving the parahydroxylation of phenylalanine to tyrosine. The abnormal enzyme is the protein fraction I of phenylalanine hydroxalase found in the liver.[6] Reduced diphospho- or triphosphopyridinenucleotide (DPNH or TPNH) is required for this enzymatic hydroxylation.[7] The abnormal metabolites, phenylpyruvic acid, phenylacetic acid, and phenylacetyl glutamine, are excreted in excess quantities in the urine.[8] The individual systemic effects of these substances in terms of specific physical abnormalities of the syndrome are yet to be discovered.

The pattern of inheritance is a simple autosome recessive with each parent being a carrier and, theoretically, one of four children being homozygous and manifesting the disease.[9] In practice this simple mendelian law is subject to change. The incidence of phenylketonuria is 1 in 25,000 to 1 in 40,000 in the general population.[10]

Patients show great variation physically and mentally. They exhibit fair skin, blond to light brown hair, and tend to be small in stature. Paine[4] described numerous associated neurologic abnormalities, especially in the severely mentally retarded children. Findings of café au lait spots, dermographia, congenital heart disease, club feet, undescended testes, and spina bifida occulta were reported in his group. He found 61 per cent to have neurologic abnormalities. One-fourth to one-third of patients have seizures, the majority occurring in the more severely retarded.[4, 10] Abnormal electroencephalograms are reported as high as 79 per cent.[4] Kreezer[11] has found what he considered a characteristic abnormality of the electroencephalogram. The manifest sign of the syndrome is mental retardation. Paine[4] and Jervis[10] have relatively large groups of patients showing the spectrum of mental retardation. Our patient fits into the unusual category of a borderline normal I.Q. of which Jervis[10] reported less than 1 per cent.

Phenylketonuries of higher I.Q. may go undetected. We feel the percentage

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In accordance with Article 1252, Paragraph No. 3 of Navy Regulations, the opinions or assertions contained in enclosed article are the private ones of the writer and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

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of these individuals will increase as more awareness of the disease is exhibited. It is hoped that by the description of our patient, psychologically and physically, more cases in this category will be discovered.

CASE REPORT

The patient is an 8¼-year-old white girl, the product of a normal pregnancy, delivery, and neonatal period. The only abnormality noted was a partial clubfoot which was casted at 18 months of age.

Physically she has been relatively normal except for height (47½ inches), which is below the sixteenth percentile. Weight is normal (54½ pounds). She has never had any dermatologic manifestations, neurologic abnormalities, or severe diseases. Her head circumference is normal.

Teachers observed that she was slow in her studies. After her father was transferred to San Diego, she was found to exhibit mirror writing and referred to the naval hospital for evaluation in September, 1957. The patient was discovered by our staff to have phenylketonuria at the age of 6 years.

A routine $FeCl_3$ test was found positive. Skull x-rays were negative. An electroencephalogram made on Aug. 6, 1958, was moderately abnormal with a basic frequency of 6/sec. and much 4/sec. activity, though the alpha rhythm was not yet present. There were no focal abnormalities. The level of development and organization is below that usually seen in this age group. Serum phenylalanine level was 36.5 mg./100 ml.[13] Urinary metabolites of phenylalanine were not obtained.

Family History.—

Father: He is 32 years of age. He is of average intelligence, and graduated from the 8th grade. He works as a handyman, and has not been tested as a carrier.

Mother: She is 32 years old, of average intelligence, and is a high school graduate. She is a carrier as demonstrated by the serum phenylalanine tolerance test.[12, 13]

Stepfather H.: He is 34 years of age, and is employed as a navy damage controlman. The stepfather is of average intelligence, and is a noncarrier.

Siblings.—

C. W.: She is 5 years old. The patient is a variation of ectodermal dysplasia (Rothmund-Thomson syndrome) with syndactylism, short stature, poikiloderma, small deciduous teeth, hemiatrophy of one extremity, esotropia, and brittle fingernails. She walked at 11 months, and began talking between the ages of 1½ and 2 years. The patient is a carrier. She is the daughter of father H.[14, 15]

D. W.: She is 3 years old. Her development was normal. She sat at the age of 6 months, walked at 11 months, and began talking between the ages of 1½ and 2 years. She is a carrier, and a daughter of father H.

Maternal grandmother: She is unstable, and has been hospitalized for psychiatric care several times for pseudo-suicidal episodes and hysteria.

Maternal first cousin: The cousin is mentally retarded; however, no other information is available.

Psychological Evaluation.—

Developmental history: V. W. sat alone at age 7½ months, and walked when she was 2 years old (inhibited because of mild congenital club defect of foot). She began to talk at age 2 years, and between the ages of 2½ to 5 years spoke in sentences with progressive clarity. She was ridiculed in school, however, for her difficulty in pronunciation of some consonants. She had many temper tantrums until the age of 6. She feared heights, including stairways, dressed backwards, and feared dogs. Enuresis occurred until two years ago. She also wished "to be fed like a baby" until that time.

Environment had a marked influence on her behavior. She was the first

born child of the mother's first marriage, the parents having adopted another sibling in the belief that they could not conceive. The father held 44 jobs in eight years, was a religious fanatic, and threatened to take this child to live alone with him in the woods. There was physical violence on several occasions by the father toward the mother and the patient. When V. W. was 2½ years old, her mother was divorced. The father is now an attendant at a mental hospital and still writes threatening letters. The mother remarried and is at present quite happy.

Testing of the child one year ago revealed her I.Q. to be 70 on the basis of the Bender-Gestalt figures. She showed no signs of mirror writing when asked to copy letters for the examiner, nor did she "mirror" any of the Bender-Gestalt figures. Each of the subtests on the WISC was consistently low, except Coding A which is a test of learning to combine certain numbers with certain symbols and involves rote memory. Upon this she achieved an average scaled score of 10. She completed each of the 45 items in less than the given time. She made several errors, but this was possibly due to the fact that she did not refer to the key after the first few symbols. She would pause at the end of each line, but when the examiner would exclaim, "Quickly, do them all," she would eagerly continue the task, apparently enjoying the challenge.

In June of 1958, the patient was retested with the WISC and again achieved an I.Q. of 70, which would place her within the borderline mental deficient category. She continued to show a talent for rote memory as demonstrated by an average score on the Coding A subtest. V. W. achieved an I.Q. of 80 (dull-normal category), on the Stanford-Binet Intelligence Test given as part of a research project conducted at another hospital.

On the basis of projective testing, it was felt that this child is extremely dependent and is seeking for love from the parental figures, but is ambivalent toward the father figure, whom she still perceives as punitive and attacking. She feels the pressure of sibling rivalry and senses her inability to compete except as a baby. She appears to be trying to achieve a satisfying contact with both parental figures.

The parents were aided in placing the child in special education classes in the local school system, where she almost immediately began to improve in her general behavior. Also, she displayed the special talent for rote learning which was noted during the testing. She not only learned her lines for a school play, but also memorized the complete play.

At this writing, a year following the child's initial visit, it appears that she is well on her way to benefiting from an improved school situation and a more stable home life. Much of this progress may well have been impossible had she been indiscriminately labeled as a "mental deficient." Though her I.Q. is borderline normal at present, we feel this will improve with favorable psychological environment.

DISCUSSION

In broadening the spectrum of a given disease, as time and knowledge progress, so does variability. When Følling[1] described phenylketonuria in 1934, the first descriptions were all those of severe mental retardation. Jervis,[9] 1939, and Munro,[16] 1947, concluded that all patients had severe mental retardation. However, Cowie,[17] in 1951, discovered a 3½-year-old child with borderline normal intelligence, and since then several authors have reported similar patients. Jervis[9] reported 0.9 per cent in his high grade category of 330 institutionalized patients. We agree with Hsia and coworkers[18] that this figure is undoubtedly higher when the general population is included. Paine[19] reported 98.1 per cent of his patients as having an

I.Q. of less than 50. His group of 106 were also institutionalized patients. Two phenylketonuries of Paine's[4] series would fall into the above category.

Low and associates,[20] 1956, speculated that because of their patient's relatively low serum phenylaluria level, there may be an incomplete biochemical breakdown of phenylalanine. Hsia and his associates'[18] case and our patient show the serum level well within range of the retarded patients. Also Jervis,[21] Borek and associates,[22] and Armstrong and co-workers[8] have demonstrated that there is generally no correlation of serum phenylalanine levels and I.Q. The major urine metabolites of phenylalanine have the same lack of significance.[8, 23] Therefore, the answer to variability probably will lie in the biochemical steps which occur after initial oxidation of phenylalanine. Here genetics may enter into end-point response.

TREATMENT

We have elected not to treat our patient with a low phenylalanine diet. Bickel and associates[24, 25] have reported encouraging results with improvement of eczema, seizures, and electroencephalograph readings. Armstrong and Tyler,[26] and Horner and co-workers[27] also found favorable results with fairly normal development in infants and very young children on the diet. However, Hsia and associates[28] reported a lack of improvement of symptoms in the older children.

Our 8-year-old patient has adjusted so well at home and in school that we feel the diet at present would be of little benefit. The patient has only minor electroencephalograph changes and is asymptomatic. Dietary control would be of little benefit in this situation, especially in view of Hsia and co-workers'[28] recent observations.

Psychologically we have found our patient to be a "phenylketonurie" and not a "phenylpyruvic oligophrenic." As time and knowledge progress, we hope that "phenylpyruvic oligophrenia" will no longer appear in the literature, for stigma of this type is likened to the diagnosis "epilepsy" and others. The term is no longer compatible with present knowledge of the disease. We are hopeful that the report of this patient may add stimulus to the broadening of another pattern of disease.

SUMMARY

1. A brief review of the literature on phenylketonuria is presented with special emphasis on the spectrum of mental retardation.

2. An unusual case of phenylketonuria was found to be of borderline intelligence after evaluation chemically, physically, and psychologically.

3. Serum phenylalanine levels did not correlate with the patient's I.Q.

4. Psychological evaluation found the patient high in ability for rote memory and gives hope that increased mental age may be obtained with continued environmental security.

5. The patient was not treated with low phenylalanine diet because of poor experimental results with use in older children, in addition to the fact that she is asymptomatic.

6. Phenylpyruvica oligophrenia is no longer correct terminology for the syndrome of phenylketonuria.

We wish to acknowledge the advice of: Dr. Clarence Glenn, Dr. Willard R. Centerwall, Dr. D. H. Greene, and Dr. E. R. Moeller.

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Clinical Pathological Conference

THE CHILDREN'S MEDICAL CENTER
BOSTON, MASS.

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THIS 6-year-old Negro girl was diagnosed as having primary pulmonary tuberculosis by x-ray and positive tuberculin tests (1:1,000) at the age of 5. Three gastric examinations were negative, but suggestive "activity" was present in the repeat roentgen films. She was treated with bed rest and then put on graded exercise. She continued to improve on this regime until the age of 5 10/12, when roentgenograms revealed an infiltration of the right lung field. She was again placed on bed rest and was given streptomycin 600 mg., isoniazid 150 mg., and para-aminosalicylic acid 4.5 Gm. each day. She remained asymptomatic for 2 months on this regime, when she developed a short febrile episode of 103° F., lasting one day. Nine days later she again became febrile, developed a sore throat, vomiting, and an erythematous rash on the face and trunk. The rash appeared urticarial in nature and was associated with marked pruritus. It then became purpuric. There was a rise in leukocyte count to 53,000 per cubic millimeter with a predominance of lymphocytes (60 per cent). Albuminuria and hematuria also became evident. She was transferred to The Children's Medical Center 6 days after the onset of her symptoms.

The physical examination on admission here revealed an acutely ill girl who was stuporous. The temperature was 99.2° F., respirations 20, pulse 88 per minute, and blood pressure 100/60 mm. Hg. She had an extensive purpuric and urticarial eruption over the neck, face, and trunk. Her face and hands were edematous. The conjunctivae were red and swollen and the oral mucous membranes contained erythematous petechial lesions. There was a generalized lymphadenopathy. The liver was felt 2.0 cm. below the costal margin but the remainder of the physical examination was within normal limits.

The laboratory data obtained at the time of admission included a hemoglobin level of 6.0 Gm. per cent and erythrocyte count of 3.98 million, a leukocyte count of 66 thousand, the differential count being polymorphonuclear cells 9, band forms 19, lymphocytes 71, and monocytes 1 per cent. The platelets numbered 26,000 per cubic millimeter, the reticulocytes 1.2 per cent of the erythrocytes. A hematocrit was 14 per cent; the sedimentation rate was 22 mm. per hour. The clotting

time was normal but the bleeding time was prolonged to 80 minutes. The urine had a specific gravity of 1.005, a pH of 5.5, urobilinogen and bile negative. The urine sediment was loaded with erythrocytes and contained 4 to 5 leukocytes per high-power field. Subsequent urinalyses gave approximately the same findings. Four days after admission the serum chemistry values were as follows: pH 7.15, phosphorus 3.4, nonprotein nitrogen 44, and bilirubin 2 mg. per cent with direct bilirubin 1.6 mg.; carbon dioxide content 14.9, potassium 4.8, and chloride 100 mEq. per liter. The serum Hinton reaction was negative, as were four blood cultures. The nose and throat cultures grew out a rare *Staphylococcus aureus,* and *H. influenzae* organisms. The stool guaiac test was negative for occult blood. The serum liver flocculation tests included: thymol turbidity 6 units, thymol flocculation 4 plus, cephalin flocculations 4 plus, and a positive heterophil at a dilution of 1:112, with a doubtful agglutination at 1:224. The serum agglutinations against typhoid and paratyphoid organisms were negative, as was a Coombs' test for erythrocytic antibodies. A preparation for sickle cells was negative. A bone marrow aspiration was interpreted as showing a highly cellular marrow with prominent large basophilic cells of the lymphocytic series, with irregular granulation in the more mature cells, increased plasma cell forms, and an adequate number of megakaryocytes. A roentgenogram of the chest revealed thickening of the straight fissure and prominence of the right hilar shadows.

The patient had a high fever, ranging to 104° F., and remained comatose throughout her hospital course. Four days after admission, her hemoglobin had fallen to 3.3 Gm. per cent, and leukocytes to 33.5 thousand, and platelets to 6.0 thousand per cubic millimeter.

Five days after admission she was given a transfusion and cortisone therapy was begun; she now developed abdominal distention. The serum chemistry values were unchanged. Roentgenograms revealed a small collection of fluid in the right pleural space, gaseous distention of the intestines, and thickening of the abdominal wall due to edema. Seven days after admission electrocardiograms contained low T waves in Lead II, consistent with hypokalemia. She required several transfusions. Eight days after admission a small hemorrhage in the left eye ground and melena were noted. Despite vitamin K and platelet transfusions, she died that day.

DR. LOUIS K. DIAMOND.*—This patient was said to have primary tuberculosis with a positive tuberculin reaction, and responded well to conservative measures. Fifteen days before she came to us, she developed a fever for one day. It seems quite likely that this was an acute infection, possibly fairly mild, although it produced a high fever. She then was well for a period of about one week, but again, 6 days prior to admission, she developed fever, rash, a sore throat, and vomiting. One wonders whether this erythema were part of a streptococcal or other pyogenic infection—yet it appears more likely that when a rash becomes urticarial and then purpuric, it is evidence of some acute

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sensitivity state developing in association with an acute infection. Now, a rash in a Negro child is often very difficult to see, and many such children with purpura as an early sign of leukemia or thrombocytopenic purpura are overlooked until they begin to have free bleeding. With the subsequent developments, we must assume that this was not just a transient mild rash but something fairly marked. Because the above symptoms were thought to have resulted from a developing drug sensitivity, the antituberculosis therapy was omitted.

The rise in the leukocyte level to 53,000, with a large number of lymphocytes, might be due to viral infection in which a lymphocytosis commonly occurs. Secondary to a drug sensitivity, we may see a very bizarre lymphocytic reaction, sometimes with lymphocytes that are large, pale, bluish, and not unlike those seen in infectious mononucleosis. In infectious lymphocytosis, too, the lymphocytes may arise to levels of 50,000 to 100,000, 80 to 90 per cent of the total cells being lymphocytes. So the possibilities of a viral infection or a sensitivity state could be entertained at this time. She also had albuminuria and hematuria. This indicates that the process was now very widespread, affecting her renal capillaries as well as those in the skin.

The laboratory data confirm some of the impressions given by the history and physical examination of the child, but confuse some of the other impressions obtained up to this point. First, she had quite a marked depression of her hemoglobin, with a less marked decrease in erythrocyte count, giving a hypochromic anemia rather than one of acute blood loss or of hemolysis. Such values go either with malnutrition, which hardly seems likely in a mildly ill child who has been hospitalized, or with more chronic blood loss. The leukocyte count was markedly elevated, with a preponderance of lymphoid cells which were not only small adult lymphocytes, but a variety of lymphoid cells, some of which were large and basophilic. Reticulocytes numbered only 1.2 per cent, suggesting that this was not a hemolytic process and also that this child's bone marrow was not reacting well to the hemorrhage. With active bleeding and a hemoglobin level of 6 Gm. per cent, one could expect a reticulocytosis of 15 per cent or higher. She may have had an inadequate marrow for a long period, and may actually have been in an aplastic state. Up to now, then, we have evidence of poor marrow response in the erythroid and platelet systems, but not among the white cell elements which are present in large numbers in the peripheral blood.

I have reviewed the bone marrow aspirate, and the young cells scattered throughout include many myelocytic as well as lymphocytic elements; megakaryocytes were not only adequate, but quite numerous. This suggests either difficulties in maturation and delivery of platelets or increased peripheral utilization, leading to the low peripheral platelet counts. The bone marrow is helpful in suggesting that this is a leukemoid reaction rather than leukemia, a finding compatible also with peripheral blood.

The lumbar puncture fluid contained 180 red cells but was normal in other respects. These cells were crenated and this would suggest petechial hemorrhage in the central nervous system,

or more likely is the result of slight trauma and the child's bleeding tendency.

The elevated direct-acting bilirubin in the serum suggests hepatic dysfunction, which is also evident in the abnormal flocculation tests and the diminished prothrombin levels.

The Coombs' test, which was done in an effort to detect an anemia on a hemolytic basis, was negative. The anemia, however, was not of the type one would expect to see with increased hemolysis, as mentioned above. Too much reliance can be placed on the Coombs' test as evidence of the presence of red cell antibody. It does show one type of red cell antibody, such as the type present in isoimmunization due to Rh antigens, or as a nonspecific antibody in only certain cases of acquired hemolytic anemia. Therefore, a negative Coombs' test should not be considered absolute proof that no red cell antibody is present. Similarly, positive tests for platelet antibodies are often not demonstrated, even when there is other evidence that platelets are being destroyed, presumably by an antiplatelet antibody.

May we now see the x-rays, Dr. Wittenborg?

DR. MARTIN H. WITTENBORG.—We have none of the earlier films on this patient, Dr. Diamond, on the basis of which the diagnosis of tuberculosis was established. Films taken here two days after admission were reported as showing a prominent right hilus. When the radiologist reports the hilar shadows as being prominent, it is usually because he doesn't know whether these represent enlarged nodes or large vessels. We see no nodularity to confirm the suspicion of enlargement of the lymph nodes. The right side of the mediastinum is a little more prominent. It could be consistent with a subsiding adenopathy, but it is not very striking. A hairline shadow runs under the right third anterior rib, suggesting that the pulmonary fissure has been involved by some inflammatory process with a residual fibrosis. The rest of the lungs are clear and the heart is normal. An abdominal film taken two days before death shows a moderate gaseous distention of a nonobstructive type, as with a mild ileus. There is some edema of the right abdominal wall, apparently extending anteriorly, suggesting an intra-abdominal inflammatory process.

DR. DIAMOND.—Dr. Auld, do we know what antibiotics were given?

DR. PETER AULD.—At first, Achromycin and penicillin, and later, Gantrisin.

DR. DIAMOND.—She did not have any aspirin for her fever?

DR. AULD.—Yes, she did.

DR. DIAMOND.—That is of some interest, in view of the fact that she had salicylates before, and, if there were any drug sensitivity, we were taking a chance using a chemical related to one of the drugs that might have precipitated her original difficulty.

Since no evidence of infection was found in this patient, and since there were indications that this might be a hypersensitivity state which might respond to cortisone, this was given, but with no improvement. Death occurred 8 to 9 days after her hospitalization here.

What can we say about the possible sequence of disease in this child?

First, without any evidence of our own of the presence of tuberculosis, we can only take the word of the experts in tuberculosis who attended this child in the sanatorium, and say that she had tuberculosis which was treated adequately until some untoward event occurred some 15 days before she came here. The terminal events might have been a spread of her tuberculosis, in spite of adequate therapy. The sudden increase in white cells, and even the occurrence of purpura might be a part of this process. This, however, would be very unusual.

Second, there is the possibility that this blood picture had nothing to do with her underlying tuberculosis. There is the rare occurrence of leukemia itself with tuberculosis. Such cases have been reported. Jaffe,[1] for example, reported in 1933 several cases of leukemia occurring in the course of treatment of patients with tuberculosis. This patient, however, failed to show predominance of one particular type of immature cell, either in peripheral blood or in the bone marrow.

Third, the occurrence of an acute bacterial infection of the throat or of generalized sepsis might have given rise to this leukemoid reaction. In infectious lymphocytosis there is a sudden increase in the size of lymph nodes and of the spelen with the presence of some 60,000 or more leukocytes in the peripheral blood. Infectious mononucleosis can do the same sort of thing and produce the same sort of change. In addition, in 10 per cent of patients it may produce a thrombocytopenic purpura. The cells in the peripheral smear were not typically those of infectious mononucleosis—they were more of the plasma cell variety.

Fourth, drug idiosynerasy must be seriously considered here. Although streptomycin may cause a serious dermatitis and desquamation with leukocytosis, and particularly eosinophilia, this type of reaction is very uncommon. Salicylates are more commonly associated with sensitivity reactions, and it is interesting that Ackroyd[2] in England has described cases of salicylate sensitivity in which the platelets or white cells are both seriously affected. One may test the patient's serum with added salicylates and platelets, or other cellular components, to demonstrate evidence of such a sensitivity state or an antibody production. Where such antibodies are formed, one can get hemolytic anemia, thrombocytopenia, or even thrombotic agglutination of platelets in the capillaries, much like the Moschcowitz syndrome.

In conclusion, it seems to me that this patient's signs and symptoms would fit the diagnosis of tuberculosis with a developing drug sensitivity. This is a very widespread and serious reaction, involving capillaries all over the body. The thromboses resulting in visceral organ damage, particularly of the liver, cause further depression of the prothrombin levels and other clotting factors, and lead in the end to massive melena. There will probably be large collections of bloody fluid in the visceral cavities.

DR. FARBER.—Thank you, Dr. Diamond.

We are delighted that Dr. Lorimer Dods of Australia is here. Dr. Dods, would you like to add anything, or disagree with anything that Dr. Diamond has said?

DR. LORIMER DODS.—I certainly would consider strongly a miliary

spread of her tuberculosis, with involvement of the bone marrow. That is a picture that I have seen two or three times. The possibilities of lupus erythematosus and sarcoidosis might be raised. In lupus erythematosis, the white cell picture is not like this, as I know it, but the thrombocytopenia, the purpura, the sex of the child, and other features of the disease are compatible.

DR. CLEMENT E. SMITH.—We had one patient, a Negro child, who had tuberculosis and what was thought to be an incidental clotting abnormality. This was explained by miliary tuberculosis, as Dr. Dods just said.

DR. CHARLES A. JANEWAY.—The rash, as described, sounds like the onset of what we call anaphylactoid purpura and the termination of the patient's life with a large amount of free blood in the bowel is not inconsistent with that diagnosis.

There are three questions to answer. The first one is: Did the child have tuberculosis in the first place? All we can say is that we suppose she did—yet it wasn't very obvious at the time we saw her. The second question is: What sort of an intercurrent disease occurred which brought her to this hospital? The third question is: What killed her?

By administering cortisone in large doses to this patient, we have confused an already obscure picture. The death of the child may be due to some virus disease like infectious mononucleosis, if that is a virus disease. It may have been made more virulent than it would have been ordinarily by the administration of large doses of cortisone.

Since she already had a hypokalemia, the administration of cortisone forced the potassium level down still further. Hypokalemia, itself, may explain the failure of the child to recover. I think it is difficult to do more than cite the possibilities here. The rash is hard to reconcile with anything except some type of sensitivity response.

DR. CHARLES PRYLES.—We had an infant recently at the Boston City Hospital who had a picture similar to this with a very marked purpuric hemorrhage involving the lower extremities, with thrombocytopenia and anemia. The only thing that we could find to fit in with this in the literature was in an article written by Sheldon,[3] of London, called "acute purpura necrotica." He believed it to represent a generalized Shwartzman reaction. In our patient there was a demonstrable infection. First, I wonder if there was any circulating endotoxin that might have set off a generalized Shwartzman reaction in this child, and, second, whether or not the cortisone in its relationship to a circulating endotoxin might have played some role in the child's death. Lewis Thomas[4] showed that if he gave cortisone before administering endotoxin to rabbits, he was able to protect them, but if he gave this within a certain period afterward, the lesions became worse.

DR. DIAMOND.—This child, during the 5 days in our hospital before she received cortisone, was desperately ill, so the cortisone did not abruptly change her condition from a relatively benign state. The cortisone apparently made no change in her condition. She continued going downhill and died three days after the cortisone therapy was started.

DR. HARRY SHWACHMAN.—Could you tell us the initial history of the tuberculosis in this child, Dr. Kulczycki?

DR. LUCAS L. KULCZYCKI.—When I was working in the North Reading State Sanatorium I knew this girl. She had a history of contact with a patient with known tuberculosis. Repeated gastric aspirations every 2 to 3 months (*over a period of 6 to 8 months*), after the initial 3 negative gastric aspirations were also negative.

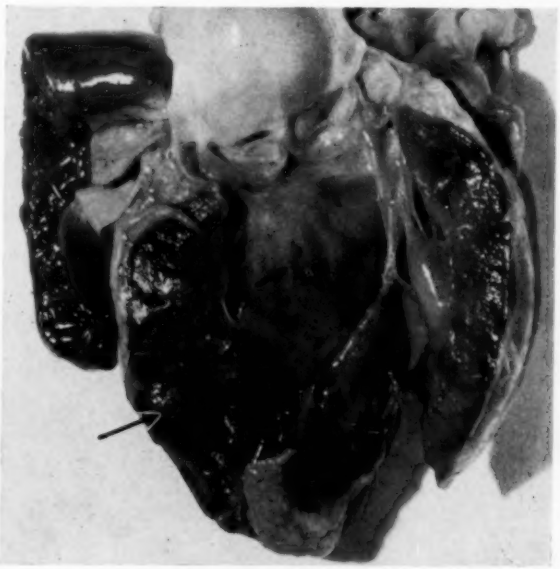

Fig. 1.—Heart. Foci of necrosis and hemorrhage are seen at arrows.

Warring and Howlett[5] studied 275 cases with tuberculosis, who received para-amino salicylic acid, streptomycin, and isoniazid. Of these, 7 were sensitized to one of the drugs. Cohen and others[6] reported 5 instances of toxic manifestations among 384 patients under treatment for tuberculosis under a similar regime. Lichenstein[7] reported 14 cases among 5,000 patients with para-aminosalicylic acid sensitivity with sudden onset of fever, skin rash, pruritus, lymphadenopathy, enlargement of the liver, jaundice, and splenomegaly. These patients also showed anemia, and lymphocytosis with the presence of atypical lymphocytosis. Positive liver function tests developed in these patients.

DR. FARBER.—What was the house diagnosis on discharge?

DR. AULD.—The house diagnosis was thrombocytopenic purpura, possibly due to para-aminosalicylic acid toxicity.

DR. FARBER.—Dr. Craig, will you tell us the postmortem findings?

DR. CRAIG.—This patient, at postmortem, had very extensive skin lesions with diffuse erythema, urticaria, petechiae, and purpura.

Microscopic examination of the skin showed a rather nonspecific change with a great deal of atrophy and

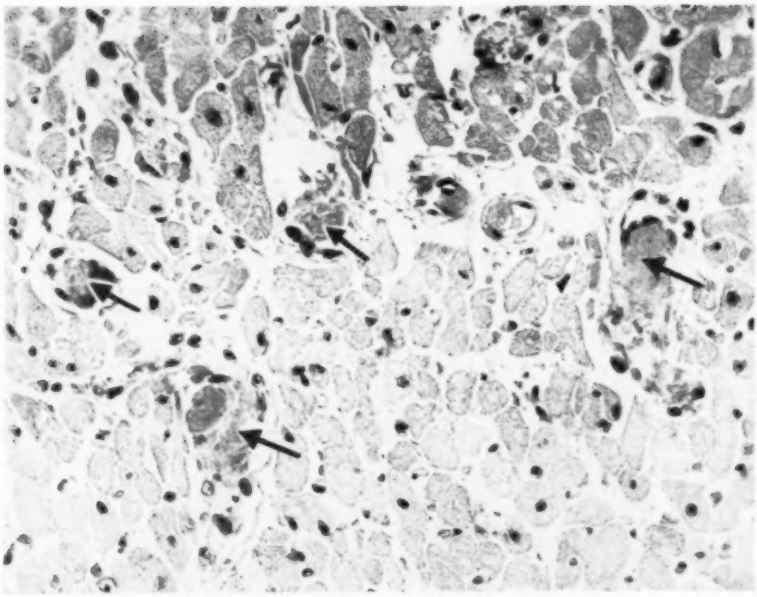

Fig. 2.—Heart. Occluding thrombi (at arrows) are present in the capillaries. (Hematoxylin and eosin; ×360.)

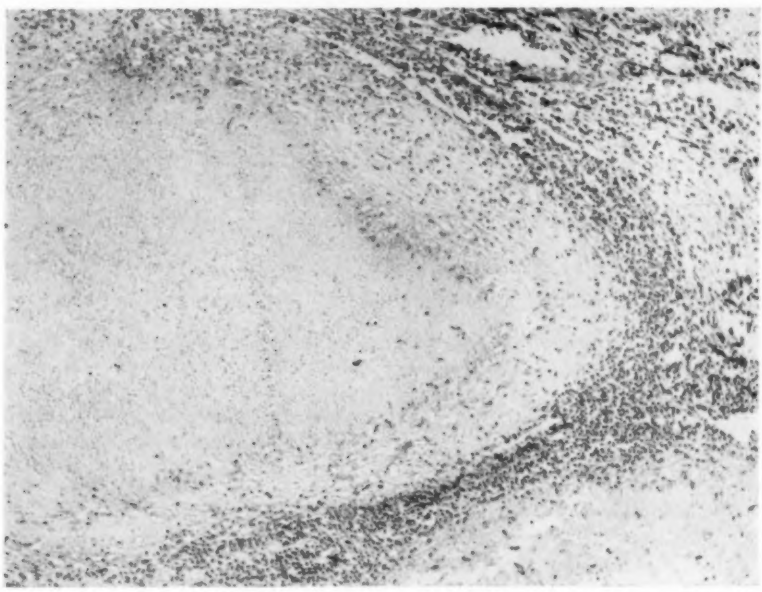

Fig. 3.—Lymph node. There is extensive caseous necrosis. (Methylene blue acid fuchsin; ×125.)

edema, and piling up of degenerating nucleated epidermoid cells on the surface, thus showing dyskeratosis and parakeratosis. There was a diffuse mononuclear infiltration in the upper dermis. This did not extend into the subcutaneous tissue. There were extensive petechial hemorrhages in the myocardium. They were associated with areas of hemorrhage and areas of myocardial degeneration. Many had been present for a sufficient length of time so that endothelial proliferation had taken place and the thrombi had actually become organized. Some inflammatory reaction occurred about

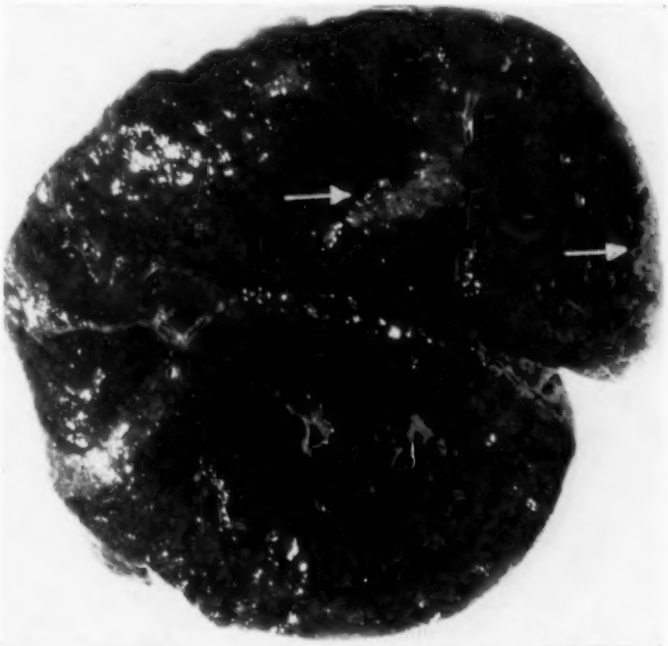

Fig. 4.—Spleen. Foci of necrosis are seen at arrows.

visceral organs, and she had 400 c.c. of fluid in her abdomen and 150 c.c. in each pleural cavity. There was no pleuritis, peritonitis, or pericarditis. The heart was enlarged by one-third, and the left ventricle was dilated. There were numerous petechiae in the endocardium and in the myocardium (Fig. 1).

On microscopic examination of the heart there were extensive thrombi in many of the capillaries and these could be found in almost every section of the the areas of regeneration of the myocardium. (Fig. 2.)

The only evidence of tuberculosis that we could find was in the hilar lymph nodes on the right, where a typical tuberculous granuloma was present (Fig. 3). This material was put in guinea pigs but we were unable to demonstrate any acid-fast bacilli. We found no primary tubercles, although we fixed the lung and cut it at 1 cm. intervals. The lungs, otherwise, contained a good deal of edema, fibrin

Fig. 5.

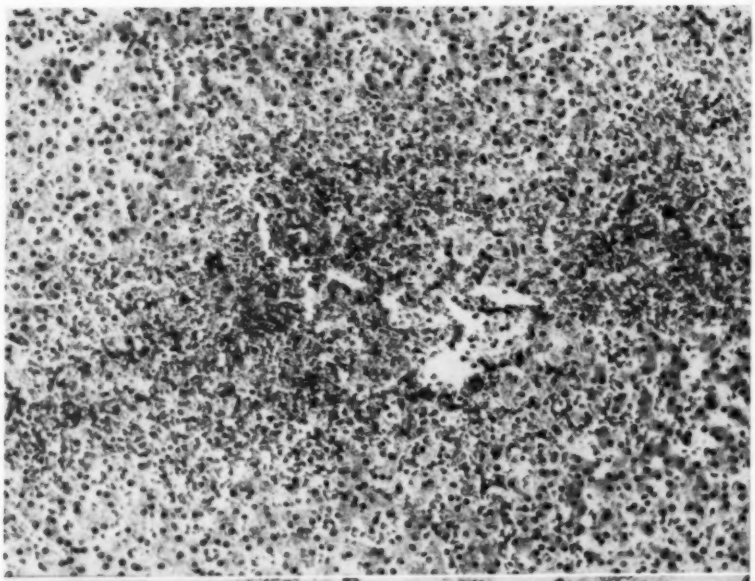

Fig. 6.

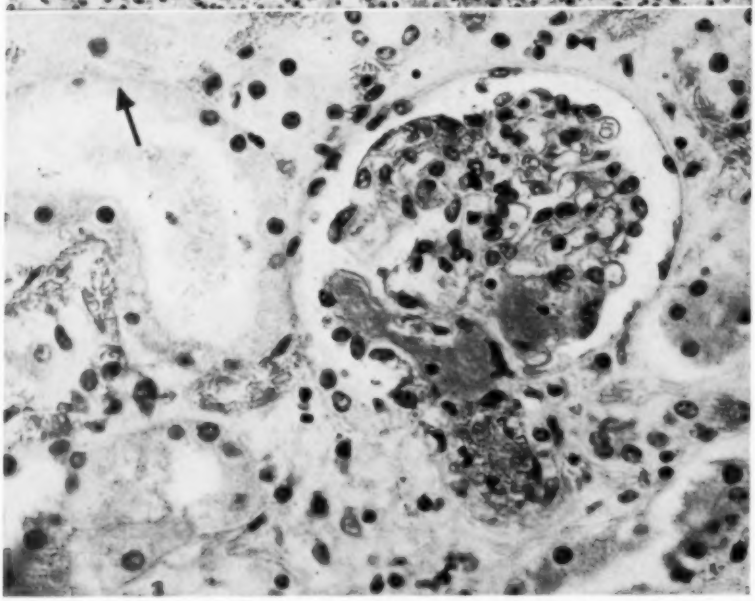

Fig. 5.—Liver. There is central necrosis and dilatation of the sinusoids. (Hematoxylin and eosin; ×160.)

Fig. 6.—Kidney. A fibrin thrombosis occludes the afferent arterioles and adjacent capillaries. There is degeneration of nearby tubules. (Hematoxylin and eosin; ×450.)

deposition in the alveoli, and alveolar septal cell proliferation. This is a rather nonspecific reaction.

The spleen was considerably enlarged and there were areas of frank infarctive necrosis on the surface and in the pulp (Fig. 4). Microscopically there was very widespread necrosis of a rather irregular diffuse nature, often intimately related to some of the penicillar arterioles. Occasionally one could find small occluding thrombi within the penicillar arterioles. In the liver there was extensive necrosis, much of it central in character although it was also mid-lobular and irregular in distribution (Fig. 5). Here again, one could find thrombotic occluded vessels.

Both kidneys were greatly enlarged (one-half again the normal weight) and showed very extensive changes, with hemorrhage and diffuse necrosis.

Microscopically there was occlusion of the glomerular capillaries with occluding thrombi and with capillary endothelial proliferation (Fig. 6). There was marked tubular degeneration in the areas supplied by the thrombosed glomeruli. Rarely were we able to see any alteration in the arterioles, though occasionally these were found. In the adrenal there was extensive hemorrhage in the cortex, and many fibrinous thrombi could be found in the peripheral sinuses, and also in the peri-adrenal arterioles. Finally, in the brain, there were subarachnoid hemorrhages and petechiae, and these were most marked in the cortex and cerebellum. There were foci of perivascular demyelination associated with occluding thrombi (Fig. 7).

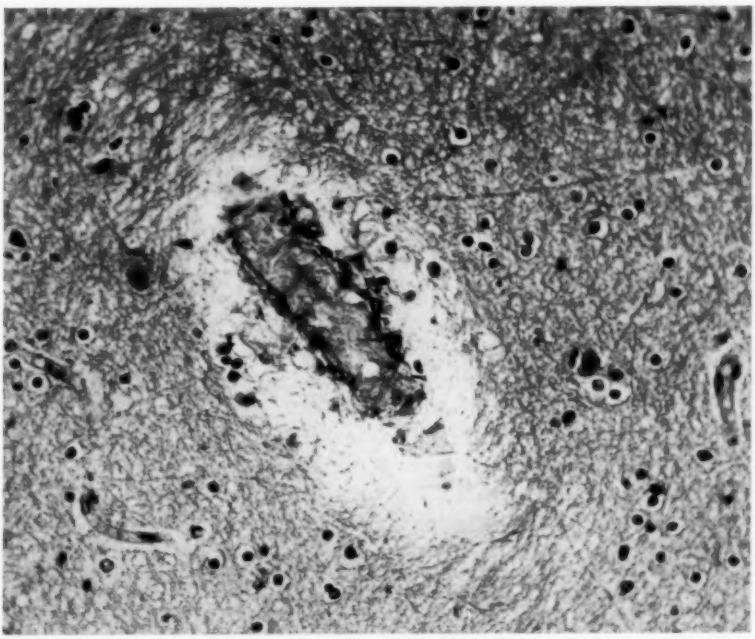

Fig. 7.—Brain. There is perivascular demyelinization in the subcortical white matter. A few inflammatory cells are present. (Hematoxylin and eosin; ×370.)

We believe, then, that this case represents, as Dr. Diamond predicted, thrombotic thrombocytopenic purpura or Moscheowitz syndrome. There is a diffuse vascular reaction and most of the pathology is related to the occlusion of these vessels and to decrease of platelets associated with hemorrhage. There are many areas of hemorrhage not associated with thrombi, although I think that there must have been independent bleeding, in addition to the areas of thrombosis.

As was indicated earlier, the para-aminosalicylic acid appears to be the villain in the case, rather than the streptomycin or isoniazid. There are no cases of this nature, as far as I know, with isoniazid. There has been one death, according to a recent article,[8] from para-aminosalicylic acid toxicity that was associated with a skin rash and agranulocytosis, although there was no thrombocytopenia. The postmortem in that case also showed, as in this child, a considerable amount of necrosis in the liver, and degeneration of the tubular elements of the kidney.

In two other cases in Norwegian literature[9] there were urticaria, erythema, and conjunctivitis, which disappeared on the removal of para-aminosalicylic acid; in another a fatality ensued.[10]

DR. FARBER.—There is no question in your mind about the previous tuberculosis?

DR. CRAIG.—I think the reaction of the lymph node is quite consistent with the diagnosis of tuberculosis, though there is no absolute proof in this case of the presence of tuberculosis.

DR. FARBER.—I think that we must be prepared, in some instances, for an almost complete disappearance of recognizable pathology in tuberculosis and syphilis after even modern treatment.

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Medical Progress

PROTEIN-CALORIE MALNUTRITION IN TROPICAL PRESCHOOL CHILDREN

(A Review of Recent Knowledge)

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MALNUTRITION is the main contributor to the very high morbidity and mortality in children in the subtropics and tropics, and recent interest in the subject has clearly emphasized two facts: (1) that it is the preschool age group, especially the younger 1 to 3 year olds, which is most vulnerable and (2) that malnutrition due to various combinations of protein and calorie deficiency forms is by far the largest problem, with the syndrome usually known as "kwashiorkor" the best-known and most dramatic manifestation.

The standard description of clinical and other aspects of kwashiorkor has been fully given by numerous authors, and need not be repeated here.[1-4] Rather, the purpose of the present review is to bring together an outline of the large amount of literature on this important topic that has been published in the last few years.

CLINICAL PICTURE

Although a number of papers, not included here, have demonstrated that kwashiorkor occurs in most tropical regions (or, indeed, anywhere the dietary and other ecological factors are suitable*), little has been added to the already well-documented account of the clinical picture of fully developed cases. Variations of the details of the clinical picture are now well appreciated and are considered to be due to such variable and inter-related factors as types of weaning—foods, length of breast feeding, presence and burden of intestinal parasites, associated infections, inherent genetic differences, the velocity of the onset and the severity of the malnutrition, and climatic influences, especially exposure to sunlight.[7]

However, Kahn and Falcke,[8, 9] in Johannesburg, South Africa, have described an encephalitis-like syndrome of unknown etiology in children recovering from kwashiorkor. The main features of the syndrome were considered to be due to extrapyramidal lesions, and included coarse tremors, postural abnormalities, exaggerated tendon reflexes and myoclonus. Complete recovery was usual.

Investigators at the Nutrition Research Laboratories, Coonoor, South India,[10, 11] have reported nonspecific

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*Kwashiorkor has been reported from Europe in recent years, as by Frontali in Italy.[5] An occasional affected child is seen in New Orleans.[6]

electrocardiographic changes in children with kwashiorkor, which returned to normal with protein therapy, and in experimentally malnourished monkeys. Similarly, Schyns and Demaeyer,[12] in the Congo, have shown that while kwashiorkor does not necessarily alter the electrocardiogram, in marked cases changes occur, particularly alterations in T waves, low-voltage curves, and bradycardia, which are reversible with treatment.

Gómez and his associates,[13] in Mexico City, have given further details of what they have termed the "nutritional recovery syndrome," which presents clinically, about 20 to 40 days after the start of treatment, hepatomegaly, associated with abdominal distention, a collateral venous circulation, and ascites. Various other features may occur, notably a "moon face." Hypertrichosis on the forehead, limbs, and trunk appears about 60 days after the commencement of therapy. The whole episode appears to be self-limiting, lasting about one month.

It is of interest that this clear-cut syndrome does not seem to have been described elsewhere, and one wonders if it may be related to the relatively high protein intake, especially the repeated intravenous protein therapy, given to some of these cases in the form of plasma and blood.

The apparent uncommonness of relapses in cured children returning to unchanged socioeconomic and nutritional conditions has been the clinical impression of workers in many, but not all, regions where kwashiorkor is endemic. This has been confirmed by Ramanathan and associates,[14] in India, as the result of follow-up studies between six months and five years after discharge.

Although malnourished children appear to have a low resistance to infection, Kahn and his colleagues[15] could find no evidence of impaired antibody production, as judged by levels of isohemagglutinin titers.

By contrast with fairly general agreement on the picture of classical kwashiorkor, the diagnostic features of the "mild" or "incomplete" syndrome and of other clinical forms of protein-calorie insufficiency are highly debatable and much under discussion. The importance of this lies especially in the field of public health, and will be discussed later when considering difficulties in formulating methods of assessing the prevalence of protein-calorie malnutrition in a tropical community.

The late sequelae of the condition have been studied by several groups of workers in widely separated parts of the world, including Coonoor and Madras, South India,[16, 17] Cape Town, South Africa,[18] and Jamaica.[19] In each investigation the difficult task of following-up kwashiorkor patients several years after treatment has shown that, despite a return to the original poor socioeconomic conditions, neither clinical evidence of cirrhosis nor histologic abnormality could be found at liver biopsy. Therefore, as stressed by Waterlow and Bras,[20] in an excellent account of present knowledge of nutritional liver damage, any relationship between the well-known fatty liver of kwashiorkor and cirrhosis in later life remains unproved in man.* It must be recalled, however, that all children investigated of necessity represent treated cases. The possibility

*This view appears to be supported by evidence from geographical pathology; as in Brazil kwashiorkor is common, whereas cirrhosis of the liver apparently is not.[21]

of long-term damage to the liver occurring in patients with "mild" or "incomplete" kwashiorkor, who never come for treatment but manage to survive to adult life, has not been investigated and, indeed, such studies would be difficult.

ETIOLOGY

It is generally agreed that protein-calorie malnutrition is the resultant of a complex of factors, social and pathological, which either limit intake (Fig. 1), prevent absorption, or increase the body's nutritional demands.

Fig. 1.—Kwashiorkor in female twin due to sharing inadequate resources of protein foods. Note all constant clinical features of kwashiorkor: growth retardation, apathy, edema, muscle wasting with some overlying subcutaneous fat, with two variable features: widespread flaky-paint dermatosis and very slight hypochromotrichia (Johannesburg, South Africa).

As noted by Suckling,[22] in Cape Town, following recovery, growth in height is maintained at the same rate as controls, though at a lower level, while growth in weight takes two years to return to a rate comparable to controls.

These body demands normally are especially high for protein during the preschool years, when growth of muscle is very rapid, owing to the characteristic change in body build, the extremities growing more rapidly than the trunk.[23]

Exact details of the diets of children developing different types of protein-calorie malnutrition are difficult to obtain, and there are few accounts based on more than inaccurate questioning of mothers. More investigations are needed in relation, for example, to critical quantitative and qualitative levels of protein, ratios between protein, carbohydrate and total calories, and data relevant to the possibility of amino acid imbalance, or even toxicity, occurring.[24, 25]

Although always mainly dietetic, several recent papers have stressed the importance of diverse etiologic conditioning factors, which can act as contributory or precipitating causes, and in part explain the fact that only a proportion of children at risk develop severe disease.[26] The importance of both acute and chronic infections, parasitic and bacterial, have been emphasized by Chandler[27] and by Platt,[28] who notes the various possible effects of protein and amino acid shortage on both of the interacting agents, the host and the invading organism.

Demaeyer and co-workers[29] have found that various infections were relevant in the Congo, especially measles and tuberculosis. Pretorius and associates[30] have investigated the onset of 205 cases of kwashiorkor in South Africa, and were of the opinion that the precipitating factor in many of their cases was a bacterial infection, including tuberculosis, shigellosis, salmonellosis, ear, nose, and throat disease, etc. However, the difficulty of being certain of etiologic correlation has been noted in a later study by the same group, who found that the incidence of possibly pathogenic *Escherichia coli*, Salmonella, and Shigella organisms was not significantly different in children with kwashiorkor and in a control group.[31]

Smythe,[32] also working in Cape Town, has made the interesting suggestion that the protein-deficient diet of kwashiorkor disturbs not only the nutrition of the child but also the intestinal bacterial pattern and the degree of bacterial growth. He postulates that this perhaps may cause diarrhea, produce competition with the host for nutrients, or liberate toxins.

Psychologic factors may sometimes be relevant in certain cultural groups. Thus, in Uganda, Geber and Dean[33] have shown that the sudden physical separation of a mother and her previously permissively breast-fed toddler, as a consequence of another pregnancy or birth, may result in a form of "maternal deprivation syndrome," with anorexia as a major feature. The lowered food intake, especially with the bulky, largely vegetable diet customary, may then precipitate the child into kwashiorkor. In this context, it is interesting to note that abnormalities in the form, frequency, and amplitude of the EEG waves have been reported in kwashiorkor patients by Sarrouy and co-workers[34] in Algiers.

The potential importance of cultural factors in the etiology has been suggested by Jelliffe,[35] who showed that although kwashiorkor in a rural area in West Bengal was mainly associated with poverty, lack of availability of protein foods, parasitic and bacterial infections, etc., in addition there were numerous "cultural blocks" tending to prevent the child from receiving the full range of foods available to him in the village. In addition, the ill effects of *recent* changes in

the social pattern, occurring as a result of partial "Westernization," may be very relevant, as with the falling-off of polygamy in Africa and the greater difficulty in the prolonged breast feeding of widely spaced children.[36]

An interesting concept is emphasized by Dr. J. Bengoa* who points out that, in some countries at least, the onset of kwashiorkor is often related to incorrect therapy by mothers, indigenous healers and, indeed, by ill-informed, trained doctors. As observed in a recent survey in Haiti,[37] this type of "therapogenic kwashiorkor" may follow overprolonged starvation in diarrheal disease, or the misdiagnosis of mild or early cases of protein malnutrition as being due only to worms, followed by overstrenuous therapy consisting of starvation, purgation (usually with locally-prepared castor oil), and various anthelminthics. Similarly, in Iran, Ghadimi[38] has described malnutrition developing as a result of sick babies being "treated" with the prolonged administration of nothing but rose-water.

The well-known tendency to seasonal variation has been re-emphasized by Carry and Gelfand,[39] in Southern Rhodesia, who have reported a considerable increase in cases during the "hungry months" (at the beginning of the wet season, when food stores are depleted and new crops not yet ready).

Fig. 2.—Kwashiorkor in 9-month-old child showing edema, flaky-paint dermatosis, severe muscle wasting with overlying subcutaneous fat (San Fernando, S. Trinidad, Federation of the West Indies).

The possibility of vegetable toxins sometimes playing a part in the etiology has been suggested by Schoenthal,[40] based on observations in animals. There seems no evidence at present of this occurring in man.

Symonds[41] has reported from Southern Trinidad that kwashiorkor is commonly seen there at a much younger age than usual elsewhere, that is, during the first 6 to 12 months of life (Fig. 2). If, as is possible and

*Personal communication.

suggested by the author, this is principally due to the falling-off of breast feeding among a group unable to afford to buy sufficient animal milk, the implications as far as the rest of the tropical world is concerned are far-reaching. The probability of similar situations developing elsewhere are increasingly likely with the spread of urbanization and technical development.[42]

In kwashiorkor, as in all forms of malnutrition, it has long been apparent that some children appear to be more prone to develop manifest disease than others living under similar circumstances. Gómez and his colleagues[43] at the Hospital Infantil, Mexico City, have found suggestive evidence of this, as a result of testing the absorption and retention of nitrogen in eight similar cases of kwashiorkor fed for a short test period on a typical poor Mexican diet of corn (maize) meal and beans, when balance studies showed considerable individual variation. That children differ widely among themselves with regard to protein needs has been reported by Stuart and co-workers,[44] and it is possible that a relatively high individual protein need may be one of the reasons why some tropical preschool children develop kwashiorkor while others do not.

PATHOLOGY

The main morbid anatomic features,[1, 3, 4] especially fatty infiltration of the liver, have been confirmed once again in a recent series of 40 autopsies reported from South Africa. In addition, in 31 of this group, microscopic evidence of bronchopneumonia or pyaemic lung abscesses was also present.[45]

Bras, Waterlow, and DePass[46] have reported the results of a large number of postmortem examinations carried out on Jamaican infants dying from protein-calorie malnutrition compared with others dying of other causes. Their most interesting finding was that panereatic pathology at autopsy may be found in children dying both from kwashiorkor and marasmus, as well as in those children dying from other miscellaneous, non-nutritional causes, whose livers showed over 10 per cent of fat.

The same workers have studied the fat and nitrogen content of the liver at autopsy in Jamaican infants dying of malnutrition (kwashiorkor and marasmus) and in a control group dying of non-nutritional disease. Fatty livers were most common in the cases of kwashiorkor, but occurred sporadically in all other groups. The amount of liver fat tended to be greatest in those who showed the least evidence of growth failure, as judged by height and weight. The total amount of liver protein in children with kwashiorkor and marasmus was reduced by nearly 40 per cent.[47]

An excellent account of present knowledge concerning the fatty liver of kwashiorkor has been given by Frenk and associates,[48] who make the following points from the literature: (1) except when maximal (i.e., of the order of 50 per cent of the net weight of the organ), there is no correlation between the fat content and the clinical condition or prognosis,[46] (2) there is a rough correlation between the fat in the liver and in the body as a whole, and (3) there is a significant association between pitting edema and fatty infiltration of the liver.[47]

Recently Gillman and Gilbert[49] have reported experiments on baboons which suggest that the fatty liver of kwashiorkor may be related to an acute widespread endocrine disturbance, resulting from the malnutrition, and involving the islets of Langerhans, the adrenal cortex, and the thyroid gland, without there necessarily being atrophy of the exocrine part of the pancreas.

A preliminary report on the pathology of the pituitary gland in malnourished Guatemalan children showed no significant histological abnormality.[50] From Uganda, Davies[51] has reported that cases of kwashiorkor there show little clinical evidence of renal impairment, but that fatty changes in the convoluted tubules form a constant renal lesion. Three Singhalese children with severe kwashiorkor dying of suprarenal hemorrhage have been recorded by de Silva.[52]

Considerable investigation has been undertaken into the hematology of kwashiorkor. The erythrocyte sedimentation rate has been found to be low to start with, and to rise in the first week with skimmed milk therapy,[53, 54] possibly correlated with changes in plasma fibrinogen.[55] Workers in Cape Town have described purpura occurring in 15 per cent of a series of children with kwashiorkor. Significant thrombocytopenia was present in only a few purpuric cases. The majority of their kwashiorkor patients showed a significant decrease in prothrombin index, attributable to deficiency of factor VII, and possibly also of factor X, and sometimes of prothrombin. These abnormalities reverted to normal with an adequate diet.[53]

Although anemia is not usually a marked or prominent finding in kwashiorkor, it is very frequently present to some degree and, as recent publications have shown, the etiology varies in different regions. That a high protein diet alone will not usually cure the anemia has been known for some time. In Jamaica, McIver and Back[56] found the peripheral blood and bone marrow changes of megaloblastic anemia, responding to oral folic acid, to occur commonly. In Uganda, iron deficiency frequently seems to be operative, as children with kwashkiorkor whose anemia is not responding to a high-protein, high-caloric diet often show a rapid response to intramuscular iron.[57] Mehta and Gopalan,[58] in Coonoor, South India, found that most cases there were due to a combination of protein deficiency, with lack of one or both iron and "liver principle." They also felt that both a deficient supply of hematinic substances and defective metabolic utilization were playing a part.

In Indonesia, Kho Lien-Keng and his colleagues[59, 60] found that anemia was sometimes partly of an aplastic nature. They felt this might arise from bone marrow insufficiency occurring as a part of the general damage to organs and enzyme systems, which results from chronic protein deficiency and superimposed infections.

This variability has been emphasized by Walt,[61] in Durban, who found some children with kwashiorkor to have a megaloblastic anemia, while in others this was normochromic and normocytic. Wadsworth[62] has pointed out the difficulty of basing a diagnosis of anemia in these cases on hemoglobin estimations, as it is possible that spurious

results perhaps may be produced by deranged body fluid distribution resulting from interference with the production of antidiuretic and suprarenal hormones. Even such an absolute index, as the total circulating hemoglobin, has been shown to be related to lean body mass,[63] which is markedly low in all forms of protein-calorie malnutrition in young children.

Jones and Dean,[64] in Uganda, have shown that kwashiorkor has a marked delaying effect on bone development, as judged by radiological examination of the hands, and that this retardation is often so considerable that an impairment of growth rate must have occurred many months before the acute manifestations of the disease. Transverse lines were also noted by these authors at the growing ends of long bones, and their similarity to the "arrested growth lines" in the bones of pigs on low-protein diets has been remarked by Stewart and Platt.[65]

More recently, Jones and Dean have reported further radiological studies in kwashiorkor indicating that the knees of affected children show numerous abnormalities, as well as a general appearance of poor calcification. They feel that radiographs of the knee may be more accurate than those of the hand as an indicator of the retardation of bone development associated with kwashiorkor.[66]

METABOLISM

The past few years have been characterized by an increasing volume of investigation into the metabolic dysfunction occurring in protein-calorie malnutrition in young children and in experimental animals.[67] In particular, research into protein metabolism, enzyme activity, and body composition (including water and electrolytes) has not only increased fundamental knowledge, but has already been of practical value in indicating improved methods of treatment. Also the research has suggested possible approaches to measuring the severity, or degree, of protein malnutrition quantitatively and especially of diagnosing less severe degrees of deficiency biochemically.

Protein and Amino Acid Metabolism.—The nitrogen metabolism of children with kwashiorkor has been studied by various workers. In the Congo, recovering cases showed a nitrogen retention proportional to the intake within a range of 0.5 to 7.8 Gm. per kilogram of body weight, both with protein of animal and protein of vegetable origin.[68] More recently, Robinson and her colleagues,[69] in Guatemala, have investigated children in the stage of late recovery (which has been termed "consolidation of cure" by Brock and associates[114]) and found that with milk protein given in amounts varying from 2.6 to 9.4 Gm. per kilogram there was an average absorption of 80.2 per cent. An episode of diarrhea in one child was associated with a drastic reduction of both absorption and retention of nitrogen. In the nondiarrheal children, the nitrogen retained per kilogram per day showed no correlation with either the protein intake or absorption.

Albumin metabolism in kwashiorkor has been studied by Gitlin and coworkers,[70] using I^{131}-labeled albumin as a tracer. The half-life during the hypoalbuminemic period was no different from that after the same protein rose to normal during recovery, so that the authors conclude that hypoalbuminemia is due to a decreased

synthesis and is not related to increased loss or destruction of albumin.

In Jamaica, Waterlow and his associates[71, 72] have studied protein metabolism by measuring changes in the composition of liver and muscle tissue. Basing their work on the known loss of liver protein in protein-starved animals, studies by these workers have demonstrated very severe losses of the same order in malnourished children, both at autopsy and in vivo using material obtained at liver biopsy. Waterlow has suggested that as malnutrition causes a more or less uniform loss of all cytoplasmic constituents of the cell it is useless to measure the protein content per unit weight of tissue. In postmortem studies, or with experimental animals, the protein loss can be demonstrated by measuring the total weight of the liver (after due allowance for fatty infiltration). With liver-biopsy material, there is no knowledge of the liver weight, and Waterlow has suggested that a ratio of cytoplasmic protein to nuclear desoxyribonucleic acid (N/DNA) might be used to gauge protein malnutrition, because there is evidence that during malnutrition the cell nucleus and, hence, DNA probably remains essentially unchanged.

However, further observations by Waterlow and his associates suggest that this concept is an oversimplification. The recovering liver shows histologic evidence suggestive of nuclear activity associated with the division and multiplication of cells. In addition, they point out that in the long-standing malnutrition needed for the development of kwashiorkor or nutritional marasmus the brunt of protein malnutrition probably falls on muscle tissue. Waterlow and Mendes[73] have recently reported changes in the ratio of noncollagen nitrogen/DNA in muscle biopsy material obtained from the pectoralis major of 18 malnourished infants on admission and several months later, after recovery. There was an increase in this ratio of about 45 per cent. Similar results have been obtained in both muscle and liver tissues in weanling rats fed on a low-protein, high-carbohydrate, poor Jamaican diet and then rehabilitated with a high-protein feeding. These results tend to support the hypothesis that the ratio of noncollagen nitrogen/DNA in muscle may be a useful index of the degree of protein malnutrition.[74]

Preliminary investigation of amino acid metabolism in kwashiorkor has been undertaken by Cheung and his co-workers[75] in three affected children, who showed a low urinary threonine output, while isoleucine was excreted in higher amounts and proportions than leucine. Figures for urinary phenylalanine were also higher than those of tyrosine. Free amino-aciduria was absent, although it appeared during recovery. In West Africa, Sénécal and his colleagues[76] examined both the serum and urine chromatographically for 16 amino acids in children with kwashiorkor and in normal controls. With the qualitative methods employed, little difference could be detected.

Garrow,[77] working in the Metabolic Research Unit in Jamaica, has reported results of a small preliminary series of metabolic studies of S^{35} methionine uptake in protein-depleted children. This type of radio-active tagging plainly represents a very fruitful line of research.

Cravioto[7] has commented that within the over-all picture of this type of malnutrition there may be more than one specific amino acid deficiency. The possibility of amino acid imbalances also needs investigation.[24, 25] With these concepts in mind, the Mexican group of investigators have started a long-term investigation of amino acid metabolism in children with kwashiorkor and nutritional marasmus. Twelve out of thirteen patients examined in a preliminary study were found to have an abnormal phenylalanine/tyrosine ratio.[7]

As the Food and Agricultural Organization[78] notes in a recent publication, the following investigations are needed: (1) the amino acid pattern in the urine and plasma, (2) balance studies on specific amino acids, and (3) load tests with tagged amino acids.

Fat Metabolism.—Some degree of steatorrhea has long been recognized as occurring in kwashiorkor. Recent studies of fat metabolism have confirmed this and shown that there is poor absorption during the acute stage,[68] late recovery,[69] and even sometimes long after clinical recovery.[79] Holemans and Lambrechts[68] believe this is to be due to faulty digestion rather than absorption. Mehta and coworkers,[79] in Southern India, have shown that in kwashiorkor patients on a low-fat diet the fecal fat exceeds the fat intake, suggesting that some of the fat in the stools is of endogenous origin.[79] Gómez and his associates[80] found that although fat absorption was poor, larger intakes were associated with greater absorption both during malnutrition and recovery.

Demaeyer and Vanderborght,[81] in the Congo, have shown that fat absorption in kwashiorkor improves from 68.5 per cent to 85 to 90 per cent during treatment. The relative percentage of fatty acids in the stools which may, within certain limits, be considered as an index of the activity of digestive enzymes, also increases and seems to indicate an improvement of the digestive processes. These workers feel that two factors are responsible for the steatorrhea: (1) faulty digestion, due to diminished enzyme production, and (2) defective absorption, possibly caused by "a biochemical lesion of the intestinal wall."

In Uganda, the serum neutral fat and esterified cholesterol have been shown to rise during treatment, perhaps as a result of fat and cholesterol mobilization from the liver. Schwartz and Dean[82] suggest that failure to mobilize fat may be a significant feature of kwashiorkor.

Water and Electrolytes.—The mechanism of the production of edema in kwashiorkor has been investigated in experimental animals by several workers. Syndromes with points of similarity with the human disease have been produced in monkeys fed on a maize diet,[83] in rats on boiled African plantains,[84] or cassava,[85] and in monkeys on a high-calorie, low-protein diet.[86]

In protein-deficient weanling rats, Heller and his associates[84] found steroids to be most effective in combating edema; while Alexander and Sauberlich[87] have reported that the edema produced in protein-deficient weanling rats could be prevented by a variety of substances, including methyl compounds and choline.

Schnieden and co-workers[85] investigated children with kwashiorkor and protein-deficient, cassava-fed rats and in both found an impaired renal

response to water and an increased virtual deuterium space (total body water).

Experiments by Gopalan and Ramanathan[86] are of especial interest. They used three groups of monkeys: one control, one fed on a high-calorie, low-protein diet, and a third on a low-calorie, high-protein diet. Response to water-load tests was more impaired in the high-calorie, low-protein group, whose diet approximated to that presumed to be most usually responsible for human kwashiorkor. It was suggested that liver damage might have impaired the normal ability of the liver to inactive antidiuretic substances.

Electrolyte metabolism in kwashiorkor has been investigated in several countries. In Indonesia, serum potassium was often found to be low.[88] In South Africa, Hansen and Jenkinson[89] found immediate and sustained potassium retention in seven infants investigated; the serum potassium was usually low, but was felt not to give an adequate idea of cell depletion.

By contrast, Jayalakshmi and associates,[90] in India, found serum potassium levels to be normal even before treatment, although serum sodium levels were low but rose to normal levels with therapy. Pollitzer and Wayburne,[91] in South Africa, found serum potassium to be low in diarrheal cases.

More recently, very exhaustive and detailed studies have been carried out by Gómez and his colleagues,[92] in Mexico City, on intracellular metabolism and homeostasis in this type of chronic severe malnutrition. They base their investigation on the thesis that these children are both structurally and biochemically different from normal well-nourished children, and that the nature and efficiency of the body's homeostatic mechanisms are markedly changed so that they react in a different manner both qualitatively and quantitatively.

The first of these important studies consisted of chemical analyses of skin and muscle. In most cases, both tissues were found to show an increase in water, sodium, and chloride, which persisted, but in a less marked form, even during clinical "dehydration." The potassium content of muscle was slightly to moderately decreased, especially in clinically edematous cases.

The skin specimens of children without demonstrable edema had comparable amounts of water, but less fat per unit of dry fat-free solids than those of children with pitting edema.[93] As Cravioto[7] has summarized it, both infants with kwashiorkor and with marasmus show biochemical evidence of edema of the skin, and it is suggested that the recognition of clinical edema depends upon the presence of a good-sized layer of subcutaneous fat beneath an overhydrated skin.[48]

The same group has investigated renal adjustment in chronically malnourished infants and has shown a significant reduction in filtration rate and renal plasma flow, most evident during dehydration.[94]

Summing up these valuable preliminary studies, it is suggested that the outstanding biochemical features of chronic malnutrition, particularly if associated with recurrent diarrhea, are extracellular hypotonicity, intracellular overhydration, and a decrease of intracellular potassium, not necessarily revealed by hypokalemia. The tentative practical suggestion is made that a hypertonic solution or, more

safely, one having a similar osmolarity with the patient's own plasma, may be required intravenously to correct this type of electrolyte imbalance.[95, 96]

Enzymes.—In kwashiorkor there is known to be a deficient production of various tissue enzymes, which are themselves proteins.[1] Recent serologic investigations have reconfirmed that alkaline phosphatase may be low (possibly related to coexistent bone growth-failure),[97] as is the serum amylase.[98]

Measurement of hepatic enzymes in liver biopsy material was initiated by Waterlow and Patrick,[99] in Jamaica, who have shown that, in malnourished West Indian infants, there is a fall in succinoxidase and nonspecific cholinesterase in the liver. More recently, Mukherjee and Sarkar,[100] in Calcutta, have shown that while hepatic catalase and alkaline-phosphatase decrease during treatment, cholinesterase is low initially and increases during the same period. In Guatemala, Burch and coworkers[101] have carried out simultaneous biochemical and enzyme determinations on both liver biopsy material and sera.

Calcium and Phosphorus Metabolism.—Balance studies in the Congo by Holemans and Lambrechts[102] have indicated that kwashiorkor has no marked specific injurious effect on calcium or phosphorus economy, as the absorption, retention, and excretion are comparable with findings in "healthy" African children.

PROGNOSIS

The gravity of the prognosis in kwashiorkor is related to various factors including the degree of weight deviation from normal, coexistent diarrhea (and water and electrolyte imbalance), and the presence of often clinically inapparent infection, such as bronchopneumonia. In addition, according to Gómez and his colleagues,[103] prognosis is not directly related to either edema or skin rash.

It is difficult to compare the mortality rates from different countries, depending as they do on the severity of the local syndrome, whether all cases are admitted or only the gravely ill, etc.; it is probably correct to say that in affected children admitted to hospital the mortality will usually range from 20 to 60 per cent. The long-term prognosis in severe, treated and mild, untreated protein-calorie malnutrition requires much further investigation; some of the few known facts regarding sequelae have been mentioned earlier.

Prognostically valuable biochemical tests are still uncertain, probably the only useful assessment of liver function in this respect is the bromsulphthalein excretion test.[104]

TREATMENT

Diet.—Treatment of kwashiorkor and of other protein-calorie deficiency syndromes of early childhood remains essentially dietetic, although recent biochemical research has given guidance and suggested certain modifications and other improvements. The basic principle of treatment is to feed the affected child with animal protein in an acceptable and easily digestible form. The mainstay of therapy, according to most authorities, remains inexpensive, widely available skimmed milk, which is given orally in small, repeated bottle feedings, or by gavage, according to the general condition of the patient. As noted by Sénécal,[105] an indwelling nasal catheter, which

can be left in situ for a day or two, is both less exhausting to the child and timesaving for the overworked nursing staff. The amount and strength of the skimmed milk formula will have to be gauged by the child's condition. As soon as judged safe, and appetite and food tolerance appear to have returned, which is usually after a week or two, an easily digestible, high-protein, high-vitamin balanced "toddler's" diet can be gradually introduced, based on the local food pattern, including such valuable indigenous milk products as the curd *(dahi)* of India.[106]

There is little doubt that if this regime is used, together with the skilful and affectionate nursing needed to overcome anorexia, most average cases of kwashiorkor will recover uneventfully, with improvement of appetite, disappearance of edema and dermatosis, and return of such signs of well-being as smiling and taking an interest in the surroundings.

A variety of modifications of this basic approach are used by different workers. First, emphasis may be given to supplying extra carbohydrate with the milk, because of its protein-sparing effect.[107] As there is the clinical impression that some cases are intolerant of sugars, ripe bananas have been so employed. The calorie content of the formula can be raised by blending in various vegetable oils, such as cottonseed oil, which are considered to be better tolerated than animal fats, such as that of milk.[109] However, the standard formula successfully employed by Gómez and co-workers,[96] in Mexico, seems to run contrary to two of these dicta, as it consists of whole (that is, full-cream) milk with 10 per cent corn syrup added.

The second point of controversy is concerned with the amount of protein required at different stages of therapy, and the way in which the milk so used can be fortified with protein or made more digestible. The range of opinion seems to be that a protein intake of between 1.3 and 3.5 Gm. per kilogram should be aimed at for the first few days or week, and that this should be increased thereafter to figures varying from 3 to 8 Gm. per kilogram or even more.[26, 96, 105]

The possible danger of too high a protein intake in a child severely depleted has been mentioned by Holt,[108] who suggests the generalization that when any kind of food is withheld for a long time, the adaptive enzyme systems responsible for metabolizing it suffer. In this context it may be noted that three entities have been described which perhaps may represent metabolic "treatment syndromes": (1) the nutritional recovery syndrome,[13] (2) the fifth-day hypoglycemic coma, noted by Sénécal[105] in children treated only with a high-protein intake in the form of protein hydrolysate, and (3) just possibly, the encephalitis-like picture described in South Africa.[8, 9]

Various modifications of milk have been suggested, including protein reinforcement with casein,[109] and supplementation with lysine (which produces no benefit).[110] Attempts to increase digestibility have been made by acidification to produce a finer curd,[111] or by the use of milk protein hydrolysate with added carbohydrate, in view of the pancreatic damage known to be present. (The last is expensive, but Sénécal is of the opinion that a shorter hospitalization will counterbalance the higher cost of therapy.[105])

In order to test the effect of various dietary regimes in causing "initiation of cure" in kwashiorkor, Pretorius and Smit[112] both employed fresh and spray-dried skimmed milk preparations, both alone and supplemented on different occasions with dextrimaltose, casein, and carob flour. No significant difference could be found with regard to diarrhea, nitrogen retention, or initiation of cure. In view of this, it is the opinion of these South African workers that skimmed milk is still probably the best treatment for kwashiorkor.[113]

However, in East Africa, a formula is preferred in which skimmed milk is reinforced with calcium caseinate and vegetable cottonseed oil, which supplies a high-protein, high-calorie intake, while avoiding the diarrheal alimentary intolerance to animal fats seen in these cases.[109]

Plainly, more comparative studies are needed. This will be a difficult task until the severity or degree of protein malnutrition in different groups of cases can be compared quantitatively and objectively. Variation both of locally significant conditioning factors and of other details of treatment, including the use, or not, of routine antibiotics, will make for difficulty in standardization.

The well-recognized clinical problem of the occasional infant with protein-calorie malnutrition, often in the form of nutritional marasmus, who fails to gain weight for days despite a reasonable intake and no diarrhea or vomiting has been discussed recently by Holt,[108] who suggests that if absorption can be shown to be adequate, a slowly improving derangement of tissue anabolism may be present.

The experimental treatment studies of Brock and colleagues,[114, 115] in South Africa, have been of great value in helping to understand kwashiorkor and its etiology. This work has shown that cures can be initiated with vitamin-free casein or with mixtures of synthetic amino acids. Thereby demonstrating that one of the essential factors in the pathogenesis of kwashiorkor is a deficiency either of protein or specific amino acids.

The successful use of vegetable protein mixtures in the treatment of kwashiorkor has been reconfirmed by Thompson,[116] in Uganda, using a soya-bean mixture. However, in this series, therapy had to be abandoned in one-third of the children because of anorexia or inability to take the large volume necessary. The importance of this type of study is probably largely in relation to prevention.

Parenteral protein therapy, with plasma or blood, should, according to most workers, be reserved for severe, recalcitrant cases, especially those with persistent vomiting, shock, or severe anemia. (Sénécal, who states that treatment of severe cases may be initiated by a single infusion of plasma, notes that the technique of Aubaniac[117] is usually used, employing the subclavian vein.)

Fluid and Electrolytes.—As has been noted earlier, much recent investigation has shown that mortality in kwashiorkor is often associated with dehydration and abnormalities of electrolyte balance which, if facilities are available, merit careful investigation and individualized correction. However, in view of the evidence of lowered body potassium in kwashiorkor, especially in relation to the very common

diarrhea and anorexia, it seems logical, inexpensive, and apparently harmless to administer potassium citrate (100 to 200 mg. per kilogram per day) orally to all cases. In early treatment, this will replenish depleted body stores and, during consolidation of cure, supply potassium for the rapid cellular increase of muscle regrowth. In Dakar, Pille and his associates[118] even suggest that 5 ml. of a polyelectrolyte solution containing potassium, magnesium, phosphate, and sulfate be added routinely to the milk feeds.

Antibiotics.—The routine use of antibiotics in the treatment of kwashiorkor is a controversial matter. Béhar and his co-workers,[111] working in Guatemala, feel that they should be employed, as infection is so common in these children and so often unaccompanied by either fever, leukocytosis, or other overt manifestations. This point of view appears to be supported by such autopsy findings as those of Campbell,[45] in Cape Town, who showed that microscopic evidence of lung infection was present in three-quarters of fatal cases of kwashiorkor. The beneficial effect of small daily supplements of both chlortetracycline and oxytetracycline in initiating cure in kwashiorkor has been demonstrated both in Nairobi[119] and Bombay.[120] Various explanations have been suggested, one being that inapparent infections are being treated.

Conversely, the clinical opinion is held by some experienced investigators that antibiotics, and indeed any drugs, supplements, or vitamins, must be used with caution and only when necessary, as harmful side effects are much more frequent in these malnourished children.

Further study is needed to resolve this controversy, and the answer may vary with the differing etiology of kwashiorkor in various parts of the world. "Urgent," obvious, and nutritionally relevant infections, such as tuberculosis or malaria, or heavy infections with ascariasis, always require prompt therapy. Probably all severe cases should be given an initial course of procaine penicillin.

Anemia.—Treatment for the anemia will depend upon both its degree and especially its etiology, as shown by hematologic studies of the blood and bone marrow. Thus, in Uganda parenteral iron may often be indicated[57]; while in Jamaica folic acid deficiency is common.[56]

Vitamins, etc.—Vitamins, iron, enzymes, and lipotrophic preparations are *not* required in initiating cure and, in fact, may be contraindicated, except in patients with "urgent" types of vitamin deficiency, such as keratomalacia which requires immediate parenteral therapy, or ariboflavinosis in which the sore, cherry-red mouth interferes with the infant's willingness and ability to take the milk diet. The possible harmfulness of unnecessary vitamin therapy has been suggested by Carvalho and Potsh,[121] who found that the administration of high doses of the B complex increased the mortality rate in kwashiorkor.

However, it is generally agreed that later, during "consolidation of cure," oral iron and multivitamin preparations should be given, while minor infections should be treated.

Results.—The biochemical results of successful treatment in uncomplicated Guatemalan cases have been summarized recently by Scrimshaw and

his colleagues.[122] As they point out, serum levels of protein, albumin, and various enzymes (pseudocholinesterase, amylase, lipase, and alkaline phosphatase), serum levels and the absorption of fat soluble vitamins, duodenal enzyme activity, and fatty infiltration of the liver will all have improved greatly within the first 7 to 10 days on oral protein therapy alone. Demaeyer and Vanderborght[123] have also reported a similar study from the Belgian Congo.

PREVALENCE

That protein-calorie malnutrition is widespread in preschool children in most tropical countries is generally agreed by all working in the field of tropical pediatries. However, in order to appreciate the full public health significance and geographical distribution of a disease, it is necessary to measure its incidence or prevalence in the community. This is especially important in the evaluation of ameliorative public health measures. Because of this, considerable thought has been given to possible field and hospital methods of measuring protein malnutrition.

As noted previously, the position is considerably complicated by the fact that different forms of malnutrition, due to the lack of both protein and calories in tropical children, result in a kaleidoscopic and bewildering variety of clinical pictures which are often difficult or impossible to classify.

Various attempts have been made to separate the major clinical syndromes. Recently it has been suggested that this group of conditions can tentatively best be termed "protein-calorie malnutrition." *A lack of protein with varying levels of intake of calories, especially in the form of carbohydrate,* appears, according to present evidence, to be mainly responsible etiologically,[124] and results, among other things, in a profound disturbance of what Allison has called the body's normal "efficient balance between fat stores and lean body mass."[107]

Based on this working hypothesis, four principal clinical syndromes have been described in Haitian preschool children[124]:

1. *Kwashiorkor* (Figs. 1 and 2), probably due to severe protein lack in rapidly growing children receiving a relatively high intake of calories in the form of starchy, largely carbohydrate foods. Constant criteria for diagnosis are pitting edema (at least in the pretibial region), a very low body weight, wasted muscles, with at least relatively "normal" overlying subcutaneous fat, and apathy as evidenced by silent, listless inertness. Some degree of "moon-face" is usually present. One or more of the following "variable" features are often found but are not regarded as necessary for diagnosis: hair changes (hypochromotrichia, sparseness, silkiness, straightness, and easy pluckability), hepatomegaly, classical "flaky-paint" dermatosis, loose stools, and signs of associated vitamin lack, especially ariboflavinosis.

2. *Incomplete, mild kwashiorkor* (Fig. 3), presumed to be the result of a similar, but less severe, diet, and perhaps only awaiting an infection or other conditioning factor to convert into the full syndrome. The criteria for diagnosis are the same as listed for kwashiorkor, save that edema is not present. It will then be appreciated that the diagnosis of this condition in the field may have to be based largely on a low-body weight and inherently

inaccurate clinical judgment of wasted muscles with relatively normal subcutaneous fat and apathy.

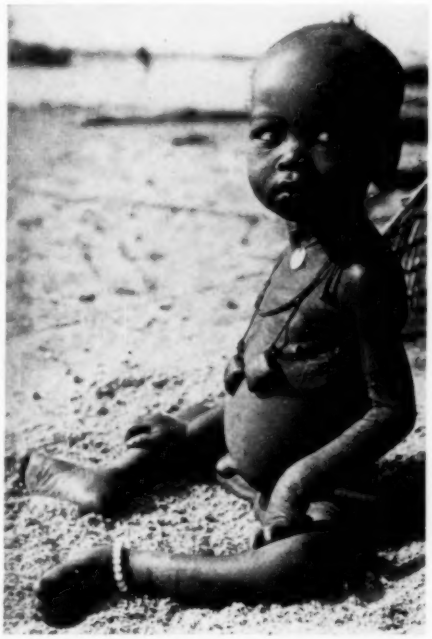

Fig. 3.—Protein-calorie malnutrition in a young child illustrating difficulty of syndromal assessment. Possibly classifiable as "incomplete kwashiorkor," with growth retardation, muscle wasting with some subcutaneous fat, sparse hypochromotrichial hair, and no edema (French Sudan, Africa).

3. *Nutritional marasmus* (Fig. 4), probably due to an extremely low intake of all nutrients, including protein. Diagnosis is based on the clinical picture of a very low weight, with marked wasting of both muscle and subcutaneous fat, without edema or significant apathy. Associated signs of avitaminoses and hair changes are sometimes present.

4. *Nutritional dwarfing*, probably due to a relatively balanced diet inadequate in both protein and calories preventing growth, but not severe enough to produce marasmus. Clinically, the patients are obviously considerably underweight and undersized while, at the same time, having relatively normal body proportions, including muscle and subcutaneous fat relatively proportional to their body

Fig. 4.—Nutritional marasmus, with marked wasting of both muscle and subcutaneous fat (Guatemala).

size. Marked apathy is not present and there are usually no other gross physical stigmata.

The differentiation of the two main syndromes kwashiorkor and nutritional marasmus has received experi-

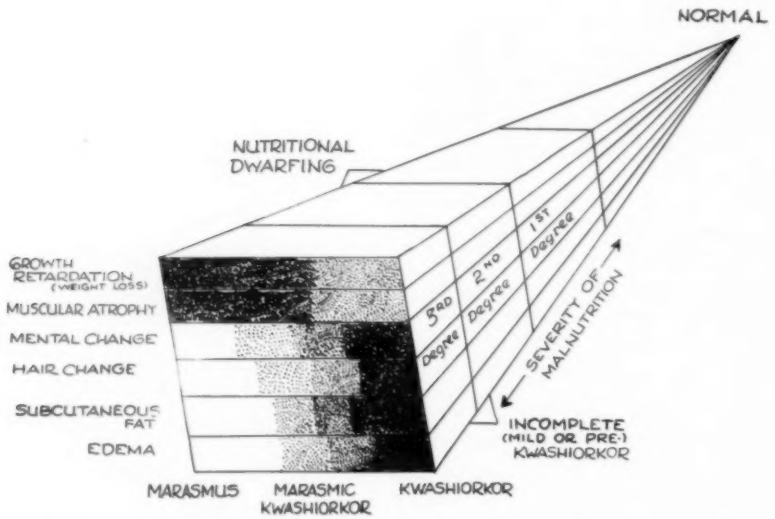

Fig. 5.—Nutritional Pyramid, showing tentative inter-relationships between various forms of protein-calorie malnutrition in tropical pre-school children. (Modified from Bengoa, and Scrimshaw and INCAP workers.)[4, 26] Base shows usual gradation of *main* features of kwashiorkor (probably due to a low-protein, high-calorie diet) → marasmic kwashiorkor → nutritional marasmus (probably due to a low-protein, low-calorie diet). Inter-relationships between classifications employed in some different countries can be identified on the pyramid: *Jamaica*.— kwashiorkor, marasmic kwashiorkor, nutritional marasmus[125]; *Haiti*.—kwashiorkor, incomplete kwashiorkor, nutritional marasmus, nutritional dwarfing[124]; *Mexico*.—first-, second-, and third-degree malnutrition.[13]

However, it must be stressed that these syndromes, which it must be noted are all related to protein deficieney, cannot be clinically defined with precision (with the exception of kwashiorkor), and many cases of malnutrition in this age group do not fit into these clinical categories.* Nevertheless, as Platt[126] has emphasized, nomenclature is important, even if tentative and impreeise, especially in view of the growing tendeney to incorrectly equate the term "kwashiorkor" with protein malnutrition (Fig. 5).

*The term "marasmic kwashiorkor" has sometimes been used to describe some of the intermediate cases.[125]

mental support recently. Heard, Platt, and Stewart[127] have shown that while piglets on a low-protein diet develop a syndrome resembling marasmus in children, striking differences in response result if this diet is supplemented with additional carbohydrate in the form of a starch-glucose mixture when a condition resembling kwashiorkor develops.

The problem of classifying less clear-cut cases is epitomized by the difficulty in attempting to define objective diagnostic criteria, especially for "mild," "incomplete," or "pre"-kwashiorkor. This has been re-emphasized by Sénécal and Aubrey[128] in a recent survey of

"malnutritions frustes" in West African infants.

It would appear that there are at least the following five ways of assessing the prevalence of protein-calorie malnutrition in a community:

1. *Vital Statistics.*—According to a number of authorities, the 1 to 3 year olds' or, usually, the 1 to 4 year olds' death rate is a useful public health guide as to the incidence of protein-calorie deficiency disease in a tropical region. Reasons for using this age group are outlined by Wills and Waterlow,[129] based on studies in Jamaica. The disadvantage is that even approximately accurate statistics are often very difficult to obtain.

2. *Biochemical Tests.*—Various biochemical tests for protein deficiency have been suggested. These include the N/DNA ratio of biopsy material from the liver or muscle which, as noted earlier, has been investigated by Waterlow and his associates[71-74] and holds considerable promise as a research technique.

Platt and Heard[130] suggest that the determination of urea nitrogen and ammonia nitrogen as proportions of the total urinary nitrogen may offer a simple method of assessing nutritional status with respect to protein. The test has the great merit of simplicity, as a single morning specimen of urine provides all the required information.

In the field, Arroyave and co-workers[131] suggested the use of the serum cholinesterase levels of Central American children, but they conclude that the test is not a sufficiently sensitive measure of protein deficiency to be of use from the public health point of view.

It is possible that suitable laboratory tests may be devised for hair samples. Thus, both Narasinga Rao and Gopalan,[132] in India, and Close,[133] in the Congo, have shown that the hair of children with kwashiorkor has a significantly low-cystine content. However, further study is plainly needed as the latter investigator also tested samples of hair sent him from Guatemalan patients with kwashiorkor and found a normal cystine content, agreeing with earlier results from Indonesia[134] and Jamaica.[135]

For a test to be of value as a biochemical indicator for use in the field, it has to be on material simply collected, transported, and tested. Possibly assessment of total and differential plasma protein levels may be useful, although even standard serum samples are often difficult to collect and transport in unsophisticated, relatively remote tropical communities, while interpretation of results may not be straightforward, owing to the interrelated effects of malarial parasites, liver damage, and intestinal helminths.

3. *Syndromal.*—Attempts can be made to assess the prevalence of protein-calorie malnutrition by discovering the percentage of children with certain approximately defined syndromes, such as the four mentioned earlier in relation to the Haiti survey (i.e., kwashiorkor, incomplete kwashiorkor, nutritional marasmus, and nutritional dwarfing). (As in all such surveys, complete circumscribed populations of rural and urban 1 to 3 year olds must be examined.)

Syndromal assessment is not at present practicable owing to the indefiniteness of the various clinical pictures. The only syndrome with a clear-cut

enough picture is kwashiorkor, in which, however, the real diagnostic criterion is one single feature, edema.

4. *Nutritional Indices.*—Certain stigmata or measurable physical signs have been used as public health indicators in mapping out the distribution of some diseases; for example, determination of the splenic index is a standard procedure in malarial survey work.

A recent important trend has been toward the evaluation of certain clinical nutritional signs which could be used as possible indices of protein-calorie malnutrition.[136]

A variety of these are under trial, including such hair signs as hypochromotrichia[135, 137] and *pelo facilmente desprendible* (easily pluckable hair),* and such measures of muscle and fat as the upper arm circumference and the biceps skinfold, as estimated with skin calipers.[124] In slightly older children, parotid enlargement has been suggested,[138] but would be of no value in the 1 to 3 year old group. The presence of so-called Muehreke's lines (paired transverse lines on the fingernails)[139] has been suggested in view of their originally reported correlation with low serum albumen levels. However, an initial small-scale investigation in South Africa could not confirm this association in children with kwashiorkor.[140]

Mention must also be made of a "numerical index of protein nutrition and function in human adults" based on a formula embodying the pulse rate in different postures, which has been suggested recently by Worrall.[141] The index is considered to be an indicator of neuromuscular reaction of body protein to standard stress. The method certainly deserves investigation in adults.

An approximate clinical grading of kwashiorkor has been proposed by Smythe,[32] in which loss of power in voluntary muscle is assessed by testing an affected child's ability to hold up the head under various circumstances.

The most useful and universally acceptable nutritional index is pretibial edema. According to most authorities the two principal, most easily measurable and objective physical signs of kwashiorkor are the low body weight and the edema. The 1 to 3 year olds' edema index would appear to give considerable public health information. The index is helpful provided other causes of edema are excluded, and also provided it is realized that as only one form of advanced protein-calorie malnutrition, kwashiorkor, shows edema, it will give an indication of only one type of severe malnutrition.

As Waterlow and Scrimshaw[142] point out, agreement is necessary concerning the essential criteria for the diagnosis of kwashiorkor and other allied syndromes. As an aid toward this end, they suggest that all clinical reports of kwashiorkor from different parts of the world should contain a frequency table of the various changes observed.

5. *Weight Deviation.*—The commonness of the flattened weight curve in the second year of life in tropical children has been recognized for some years, and its significance in relation to the nutritional "danger period of weaning" appreciated.[2, 143] In some

*Dr. J. Bengoa: Personal communication.

ways, as an extension of this realization, the Mexican school of nutritionists, under the direction of Dr. F. Gómez,[13] has for some years advocated classifying the malnutrition of early childhood into categories or degrees depending upon the percentage deviation of the weight below the average for the group (i.e., first degree malnutrition from 75 to 90 per cent, second degree from 60 to 75 per cent, and third degree below 60 per cent).

However, the Gómez classification plainly does not differentiate between the different clinical *forms* of malnutrition, that is, between the various syndromes. Although, and of as much importance, it does permit an approximate grading as to prognosis. Thus, although children with third degree malnutrition in a village will usually comprise both cases of kwashiorkor and nutritional marasmus, all will be seriously ill children with a poor prognosis. In fact, in some situations, the classification by weight may aid in formulating public health policy as to the disposal of malnourished children detected in the health clinics.

This classification is undoubtedly one of the most important devices for measuring the public health significance of protein-calorie deficiency disease in this age group, because in each syndrome a low-body weight is a constant finding. In addition, differentiation into the three degrees permits a grading of the nutritional status of a preschool-child population which cannot be achieved in any other way.

It has been the experience of the writer that the simplest field method of assessing the prevalence of protein-calorie deficiency in preschool tropical children is by a combination of (a) the edema index, (b) the Gómez weight classification, and (c) possibly the low arm circumference index.[124] The apparatus required for these tests is very simple and a junior staff can easily be trained in their use.

Other possible parameters, based on syndrome, subcutaneous fat, calculated muscle circumference, and easily pluckable hair, may give valuable ancillary information, but either require more elaborate methods and much greater expenditure of time, or are based on standards which are, at least at present, even more difficult to define. The widespreadness of protein-calorie malnutrition, as indicated by field surveys using such nutritional indices as these, is shown by recent results in Haiti.[37] This investigation showed an over-all edema index in 1 to 3 year old children of 7 per cent, together with other evidence suggesting that in the region of two-thirds of this age group were suffering from protein-calorie malnutrition of some degree.

PREVENTION

The long-term prevention of protein-calorie malnutrition in early childhood is a highly complex matter. This problem is actively engaging the attention of such international organizations as WHO, FAO, and UNICEF, as well as national governments.* Plainly, the subject can range, according to the perspective of the observer, to include measures to raise the general standard of living, adult education, family planning, etc. These cannot be discussed

*Indications of the interest in this subject are emphasized by five reported meetings on relevant topics held in various parts of the world in recent years: Joint FAO, WHO, and Macy Foundation, Human Protein Requirements and their Fulfilment in Practice, Princeton, 1955; University College, Ibadan, Nigeria, 1957; Nutrition Society, London, The Nutritive Value of Proteins, 1957, and on Fish, 1958; and the New York Academy of Sciences, Protein Nutrition, 1958.

here, although mention should be made of attempts to improve a country's yield of protein by such measures as popularizing the pond culture of fish (especially the rapidly breeding *Tilapia mossambica*), and by tropical dairy farming. (The latter includes the use of new breeds of cattle, such as the Jamaica Hope, which are better adapted to withstand both hot weather and tropical disease, and also have a relatively high milk yield.)

Much further investigation is needed into numerous theoretical and practical aspects of protein metabolism in children, including the measurement of actual requirements (both quantitative and qualitative at minimal, "safe," optimal, and satisfactory levels), and the investigation of local protein foods, especially of vegetable origin (by amino acid analysis and by animal and human feeding trials). The use of protein-rich substances which at the present are discarded, including processed peanut press-cake and fish flour, is under trial in various countries. Also, the possibility of being able to employ amino acid supplementation of various staple flours is a theoretical approach, requiring much further investigation at all levels.

On a more obvious pediatric plane, three approaches need emphasis:

1. *Organization of Child Health Services.*—It has become increasingly clear in the last ten years that child health services in tropical regions of both so-called curative and preventive types need to be organized, planned, integrated, and expanded. Considerable interest is being shown in trying to formulate the most suitable organization of child health services for individual tropical countries. It is realized that this will vary not only with the local child health problems, but with such factors as the cultural background, finances, and medical personnel available.[144-148]

2. *Education of Medical Personnel.*—In many areas, one of the most important approaches to the prevention of protein-calorie malnutrition is by means of educating medical and paramedical personnel to the understanding of the major significance of child morbidity and mortality in tropical regions, and especially to the impact of malnutrition in this age group. In particular, the clinical appearance at an early stage and the prevention and treatment of the major syndromes, especially kwashiorkor, need to be widely known, not merely at a country's research centers, but also by all personnel practicing in the field, in order that at least the "therapogenic kwashiorkor," discussed previously, can be avoided.

3. *Health Education.*—The most promising line of approach would appear to be via health education of the population as a whole and particularly mothers, especially in maternal and child clinics, in children's hospital wards, and in the homes by such personnel as public health nurses.[149] Methods of doing this are under much discussion. However, basically, a simpler, more "person-to-person" approach, with the active participation of mothers, is more likely to yield a real change than the remote didactic methods employed some years ago.[150] A particularly promising experimental approach is that evolved by Dr. J. Bengoa* who suggests that small units

*Personal communication.

attached to tropical child health centers might be developed both to rehabilitate relatively early cases of protein-calorie (second-degree) malnutrition, and to use this occasion for health education for mothers.

tance in lessening these "conditioning" factors.

Methods of infant feeding advocated in health education must be based on a clear understanding of local economic realities (Fig. 6), systems of child

Fig. 6.—Kitchen scene in lower socioeconomic group, illustrating the need to appreciate limited local home economics in planning health education in such fields as infant feeding (Indonesia).

The content of health education aimed at preventing protein-calorie malnutrition will obviously be mainly concerned with improving methods of infant feeding. However, the reduction of parasitic infection, especially ascariasis,[151] diarrheal disease, and general infectious disease, including tuberculosis,[152] is of obvious impor-

care,[153] and particularly patterns of infant feeding and local food ideologies.[35, 154-157]

Better use of available foodstuffs by means of locally meaningful home economies is a practical approach to the problem.[158] Also, attempts to base the teaching of infant feeding on such practical, but scientifically based, ideas

as the simultaneous feeding of two mutually complementary plant protein foods given as a mixture (often of cereal and legume),[2] and the avoidance of starvation in diarrheal disease.[159]

vention of the spread of new injurious food habits, which unfortunately often appear to be associated with urbanized technological development. These may include the use of overmilled rice and

Fig. 7.—Uneventful prolonged breast feeding in lower socioeconomic East Indian mother (Mona, Jamaica, Federation of the West Indies).

Powdered skimmed milk has been distributed widely in large scale attempts to prevent protein-calorie malnutrition, often free or subsidized by various agencies. Although often of value, this approach is much more complex than at first apparent, and its advantages and disadvantages must always be considered in the particular situation.[2] It is *always* of *much* less importance than health education based on the use of local, customary, already available foods.

As well as attempting to modify traditional methods of infant feeding, nutritional health education in this context is also concerned with the prevention of the spread of new injurious food habits, which unfortunately often appear to be associated with urbanized technological development. These may include the use of overmilled rice and flour, the consumption of carbonated beverages, and, most important of all, a falling-off in incidence of breast feeding.

Breast feeding is customary and almost universally successful among most tropical peasant mothers (Fig. 7). Its importance is shown by the usual excellent growth during the first six months of life, and the usual absence of protein-calorie malnutrition in the first year of life. The protein content of breast milk from these poorly-fed mothers is now well recognized to be normal, even in late lactation.[160] The amino acid composition, including the methionine concentration

of milk from African mothers, has been shown to be within the same range as for well-fed Caucasians.[161, 162] The yield in late lactation is not insignificant; for example, Gopalan[163] has found that mothers in South India were producing some 12 oz. daily between the eighteenth and twenty-fourth months of lactation. (In fact, the only difference between the breast milk of well-fed English and poorly nourished Congolese and Indian mothers that has been demonstrated in one investigation is in the curd: whey protein ratio, the significance of which is not known.[164])

As Gopalan[165] rightly states, the satisfactory situation with regard to prolonged lactation obtained among poor tropical communities must be considered a most valuable asset, to be preserved, protected, and, if possible, augmented. With the latter in mind, investigations were carried out to determine the effect of locally traditional galactogogues and of protein supplementation with skimmed milk on the output of breast milk in various stages of lactaction in poorly nourished Indian women. Preliminary findings showed no increase in yield, although the desirable effect of additional protein intake on the pregnant woman's nitrogen balance has been shown by the same group of workers.[165, 166] A full account of the major findings to date of these important long-term studies on lactation in poor Indian communities has recently been published by Gopalan.[167]

Despite the prophylactic importance of breast feeding, prolonged up to about two years in most lower socioeconomic groups in the tropics, there is mounting evidence that the falling-off of breast feeding, which appears to have swept across the Western world in the last fifty years, is also occurring among the well-to-do and even, to a lesser extent, among the less privileged poor groups.[41, 42] As noted by Welbourn,[168] in East Africa, in a paper aptly titled "Bottle feeding: a problem of modern civilization," the effect of this trend in tropical countries with completely inadequate supplies of animal milk, poor standards of hygiene, and low levels of maternal education can only be disastrous. One of the basic aims of nutritional policy in relation to the protein-calorie malnutrition in tropical regions should be based on the realization of the danger of this trend and on a consideration of methods for preventing its spread.

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Comments on Current Literature

RUBELLA DURING PREGNANCY

Since 1941, when Gregg[1] first reported the relationship between German measles (rubella) in the pregnant woman and the occurrence of congenital malformation in her offspring, the physician has been faced with the very practical problem of management in the patient who has had known exposure to rubella during pregnancy, or who develops clinical manifestations of this disease early in pregnancy. The rubella syndrome in offspring of women who have experienced German measles during pregnancy is well established, and has been verified by a number of careful clinical studies. On the basis of Gregg's retrospective studies and those of some other observers, the incidence of malformation seems extremely high. For example, Gregg reported an 80 to 90 per cent incidence of congenital malformation where rubella complicated the first trimester of pregnancy; a 21 to 78 per cent incidence following infection in the second trimester; and from zero to 20 per cent in the third trimester. Gregg's studies were retrospective in type, originating with the damaged infant. In recent years prospective studies have been undertaken with the result that these high incidence rates have been altered significantly. Such prospective studies, with subsequent examination of the newborn infant, indicate that maternal rubella infection in the first trimester may be followed by congenital malformation in 10 to 12 per cent of the cases followed. Apparently, there is very little risk of the rubella syndrome resulting if exposure to rubella or clinical manifestations of the disease occur during the second or the third trimester.

Greenberg and his associates[2] have been interested for some time in the frequency of defects as evaluated by the prospective type of study. Recently, one group reported by them comprised 104 cases of maternal rubella occurring in the first three months of pregnancy; of these 104 cases, there were 48 in which therapeutic abortion was considered advisable; in ten cases of the 104, it was not possible to follow the patient. In the remaining 46 cases, 28 of the mothers gave birth to normal infants; 12 mothers had spontaneous miscarriage; three infants were stillborn; and three infants developed congenital malformations: that is, three of 31 liveborn infants, or about 10 per cent. At the Eighth International Congress of Pediatrics in Copenhagen, in August, 1956, Lundström[3] reported extensive survey studies of the prospective type. His findings are in accord with those from other such studies, that is, malformations occurring after rubella infection in the first trimester of pregnancy in from 9 to 12 per cent. In a control group of pregnant women, comparable numerically, who did not acquire rubella, the incidence of malformation was only 1.6 per cent. On the basis of this unusually well-organized survey, risk of fetal damage from rubella contracted in the first trimester was estimated as a ratio of 6:1 as compared with that in uncomplicated pregnancy.

In spite of this re-evaluation of the incidence of fetal damage, which has been the result of the prospective type of study rather than the retrospective approach employed earlier, the problem remains and is invariably a difficult one for the clinician to handle, requiring thoughtful consideration in each individual case. In the May, 1958, issue of *Neurology*, an unusual case report appears which is pertinent in this connection. This report, from the National Institute of Neurologic Diseases and Blindness by Dekaban, O'Rourke, and Cornman,[4] describes in detail the case of an 8-year-old boy who was damaged severely as a result of rubella infection in the mother. This boy was the firstborn of a young mother who developed severe rubella at the end of the fourth week of gestation, and had to be confined to bed for one week. Description of the clinical course of the mother's rubella would indicate that this was an unusually severe disease. The infant was born with multiple defects, giving evidence of a "very profound disturbance of embryonic development." Of the fifteen pathologic lesions generally recognized as the result of maternal rubella infection early in pregnancy, this child showed eleven characteristic clinical manifestations, including cataract, congenital heart, deafness, mental and physical retardation, etc. In reviewing the literature pertinent to this case, the authors were impressed by the "occurrence of more severe abnormalities during the earliest stages of pregnancy and the substantial decline of incidence of malformation after two to three months of gestation."[4] It appeared worthwhile to them "to analyze the frequency with which the abnormalities in various organs are encountered relevant to the different stages of gestation."[4] Accordingly, these authors selected for analysis 108 cases from published reports of patients who developed rubella during pregnancy, and whose history as to the stage of pregnancy when the disease occurred was considered to be reliable. On analyzing these 108 cases in detail, it became apparent that the highest incidence of three major abnormalities, cataract, congenital heart disease, and deafness, occurred when rubella complicated the first four weeks of pregnancy. Fetuses exposed to maternal rubella between the fifth and tenth weeks of gestation still showed frequent occurrence of these malformations. From the tenth week on, there appeared to be a rapid decline in fetal susceptibility, so that the incidence reached a low level after fourteen weeks of gestation. No instances of congenital abnormality were encountered when exposure of the fetus to rubella occurred after 20 weeks of gestation. From these findings, which are presented graphically in an objective figure, emphasizing the importance of the time-exposure relationship, the authors concluded that the highest incidence of three of the most important congenital anomalies, cataract, deafness, and congenital heart disease, occurred when rubella complicated the pregnancy within the first five weeks of gestation.

A re-evaluation of the rubella problem from the standpoint of prevention was attempted recently by Krugman and Ward,[5] whose interest in this subject has extended over a period of years. Equivocal results concerning the efficacy of gamma globulin in the prevention of rubella prompted these authors to study the levels of neutralizing antibody in ordinary gamma globulin, in convalescent rubella plasma, and in gamma globulin prepared from plasma of patients convalescent from rubella. In this unusually clear-cut study, a serum pool previously shown to contain active rubella virus was used as a basis for serum-virus neutralization tests in human subjects. Four groups of individuals, six in each group, were inoculated intramuscularly with appropriate mixtures of active virus and serum: active virus from the

original rubella serum pool plus normal human serum free from rubella antibodies; active virus plus ordinary gamma globulin; active virus mixed with convalescent-phase plasma; and a mixture of active virus with convalescent gamma globulin. In the group receiving active rubella virus plus normal human serum as inoculum, five of the six individuals developed clinical rubella. Of the group who received rubella virus plus gamma globulin, one of the six developed clinical rubella; of the group receiving as inoculum a mixture of active virus and convalescent-phase serum, one of six developed rubella; and in the group receiving active virus plus rubella convalescent-phase gamma globulin, none of the six showed signs of clinical rubella.

These results show clearly the presence of neutralizing antibody to the virus of rubella in ordinary gamma globulin, in convalescent-phase plasma, and in convalescent-phase gamma globulin, and under the conditions of this study, can be interpreted as indicating the relative efficacy of these preparations in the prevention of clinical manifestations of the disease. That the rubella antibody level to be found in ordinary gamma globulin varies widely from sample to sample has been well recognized for a number of years. In one of the epidemic studies made by Korns,[6] this range of variability was considerable: from no protection against German measles to a significant reduction in its occurrence in susceptible contacts. Thus, in attempting to answer the question of gamma-globulin prophylaxis on exposure, Krugman and Ward[5] recommend that as soon after exposure as possible, all pregnant women in the first trimester who have no known history of rubella be given at least 20 ml. of gamma globulin intramuscularly. If rubella convalescent-phase gamma globulin is available, a dosage of 10 ml. administered intramuscularly is considered adequate. Early administration of gamma globulin in adequate amount is important, since rubella can occur without rash, and since damage to the fetus may be out of proportion to the clinical manifestations observed in the mother. The probable risk of injury to the developing infant would be less in a mother who receives immune substance early and in an adequate amount.

With respect to the advisability of therapeutic abortion in women who develop clinical rubella during pregnancy, the conscientious physician is often faced with a difficult decision. As Krugman and Ward[5] point out, this important decision must be based on many factors, and each case must be individualized carefully. It would seem, however, on the basis of the statistical analysis by Dekaban and his associates[4] that in the very early weeks of pregnancy, before the fourth week, the fetus is extremely susceptible to serious damage from rubella infection in the mother, and actually the damage may be done before the mother is aware that she is pregnant. Patients in this category would appear to be likely candidates for therapeutic abortion. From the sixth to the eighth weeks of gestation, the decision as to whether this therapeutic procedure is indicated could be answered in the negative more easily. Certainly patients who develop rubella beyond the twelfth week of gestation would not be advised to terminate the pregnancy.

In general, the most satisfactory approach to the problem at present seems to be as follows: A woman in early pregnancy with no previous history of rubella who has known exposure to the disease should receive immune substance early and in large amount. In most parts of the world the antibody-containing blood product readily available would be gamma globulin: dosage, 20 ml. intramuscularly. Convalescent-phase plasma or convalescent-phase gamma globulin are preferred to ordinary gamma

globulin, and should be used whenever they are available: approximate dosage, 10 ml. intramuscularly. The advisability of exposing young girls to rubella merits reiteration, especially since one attack of this benign disease of childhood is followed, as a rule, by durable immunity which will protect them throughout the childbearing period. Safe measures for active immunization against rubella, undeveloped as yet, would seem to offer a promising means of control in the future. Despite the general consensus that the risk of congenital malformation following maternal rubella is less than earlier estimates made some years ago would indicate this risk is still a real one, often with tragic consequences for the individual and his family. Careful studies such as those being reported currently are of value in helping the clinician to make a wise decision.

RUSSELL J. BLATTNER

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Correspondence

Dear "Bill Nelson":

Having just read Borden Veeder's Hail and Farewell in the December issue of the JOURNAL, I cannot refrain from writing you a line or two about *"amicus meus summus et popularis."*

When I came to St. Louis in 1920, . . . I met Borden, and happily too, McKim Marriott, Philip Jeans, Jean Cooke, Sam Clausen, and their *Morgenstern*, Alexis Hartmann. Verily, these men gave a superlative demonstration of How to Be Nice to a Newcomer. . . .

In wishing you *Bon Voyage*, this Old-Timer wishes B. S. V. many more years of service to our specialty and to the community which he has indeed graced.

Niemals Veeder? Ach, nein, nein!
Niemals soll verboten sein!
Borden, it's not Good-bye we're sayin',
But a loud, heartfelt Auf Veedersehen.

PARK J. WHITE

St. Louis, Mo.

To the Editor:

I would like to tell you how amazed I was at the opinion expressed by Dr. Ellen MacKenzie, when she wrote the following words, "Despite the great frequency of this problem, particularly in the last half century, there is little of anorexia as a separate difficulty in recent literature or textbooks. . . ." (J. PEDIAT. 53: 187, August, 1958.)

In fact, anorexia in children is, by now, well-known among all practitioners in France thanks to numerous publications and studies. French pediatric textbooks contain long explanations on this subject; where one can have knowledge of what Dr. MacKenzie has so correctly demonstrated in her article, so that we see less and less of these cases in our hospital consultations, and then only the most difficult cases.

I send you as an example, a reprint of some work on this subject which I did with my collaborators over eight years ago (Faim et appétit. La Semaine des Hôpitaux de Paris, Vol. 26, number 11, February 10, 1950). . . .

All this proves that communications between doctors who write in different languages are insufficient and specifically that French literature is little known in the States. May I add this: Our young postgraduate students go a great deal to the United States, where they receive admirable training, which is of great value to them. . . . There would be reciprocally great benefit . . . for American postgraduates to come to the Old World and examine our work. . . .

PROFESSEUR ROBERT DEBRÉ

Paris, France

To the Editor:

. . . I should have specified more clearly that the discussion was limited not only to American literature, but to the patients seen and methods used in a single area of the country. . . .

I should be interested to hear from pediatricians in other countries or cultures on the different facets of anorexia they have observed.

ELLEN P. MACKENZIE

Gretna, La.

To the Editor:

On the effects of prochlorperazine (Compazine), Jabbour et al. (J. PEDIAT. 53: 153, August, 1958) state that a daily dose of 15 mg. or less is recommended for a 1-year-old child. I believe that no dose can be recommended since individual idiosyncrasy to the drug is probably the main factor.

I recently treated a 1-year-old child with Compazine. The child received 5.7 mg. of

the syrup in 3 doses. The mother noted that the child was somewhat drowsy after the second dose but gave the third dose before bedtime.

On examination in the morning, the child had an encephalopathy with a startling resemblance to Parkinson's disease. No therapy was instituted. In 24 hours, the symptoms were appreciably less and after 48 hours the child was apparently normal and has remained so.

MILTON MARCUS

New York

To the Editor:

The recent article "Flora of the Umbilical Stump" by Fairchild, Graber, Vogel, and Ingersoll in your JOURNAL (53: 538, November, 1958) shows an alarming incidence (80+ per cent) of newborn infants having an umbilical cord flora of coagulase-positive *Staphylococcus aureus* by the fourth day of life. This is a disturbing finding even though the authors reported no associated increased incidence of complicating staphylococcal infections. Studies under progress at DeWitt Army Hospital, attempting to find the best means of preventing infection of the umbilical cord stump, suggest that Fairchild's findings may not apply to all nurseries. In our first study, infants born on odd days had their cords and cord-cutaneous junctions cleansed with 70 per cent isopropyl alcohol once every 8 hours. Infants born on even days had similar cleansing with Jellard's triple dye solution (Pediatrics 21: 858, May, 1958). At the time of discharge, aged 4 or 5 days, the cords were examined and graded: 0, if dry; 1+, if slightly moist; 2+, if moderately moist; 3+, if exudate or blood was present; and 4+, if it appeared infected. The proportions in each category were virtually identical for both preparations. Of 257 infants observed, 4 had 4+ cords and 36 had 3+ cords. Cultures were taken on 31 of these 40 cords. The organisms and the frequency with which they were found are recorded below:

Escherichia coli	16
Aerobacter aerogenes	5
Staphylococcus aureus	4
Proteus vulgaris	4
Pseudomonas aeruginosa	1
No growth	1

We are now comparing 70 per cent alcohol and a 10 per cent tincture of Wescodyne, and in addition we are now using Wescodyne 75 p.p.m. for all cleansing in the nursery instead of soap and water or alcohol. In this study the proportion of 3+ and 4+ cords has dropped from 15 to 6 per cent, but the pattern of bacterial cultures has not changed. In this study *Esch. coli* has been found 4 times. *Staphylococcus albus,* coagulase-negative *Staphylococcus aureus, Aerobacter aerogenes,* Pseudomonas, and Proteus have each been found once. In 2 instances no growth was obtained on culture.

Only 10 per cent of these 42 cultures of infected and potentially infected umbilical cords revealed *Staphylococcus aureus.* During the 4 months of our study there have been no neonatal pyoderma, breast abscesses, or diarrhea, but one infant, aged 14 days, had a septicemia from *Esch. coli.*

The differences in the structures of these studies do not appear to be sufficient to account for the differences obtained. It is probable that the factors affecting infectivity and resistance may vary greatly at different temporal and geographic planes. Similar studies will have to be done in many nurseries before the normal, or abnormal, flora of the umbilical stump can be ascertained. Both of these studies emphasize the importance of individual technique in caring for the newborn infant to prevent cross-contamination.

WARREN J. WARWICK
Captain, MC,
and
SAMUEL R. LEAVITT
Captain, MC

To the Editor:

I am writing concerning the publication of the article by Wheeler, Plotkin, Fromme, and Smith in THE JOURNAL OF PEDIATRICS 53: 571, November, 1958. I believe that the paper is inconsistent, inaccurate, and unscientific, and that it does a great disservice to those in medicine who are trying to bring order out of chaos in regard to the administration of antibiotics.

To enumerate all the defects . . . in this study would require considerable time. Accordingly, I intend only to point out a few of the more obvious. . . . I should like to challenge the duration of administration

of penicillin. The authors quote Breese and Disney on the employment of penicillin V in the treatment of streptococcal infections. They do not point out that the effectiveness demonstrated by Breese and Disney was noted when the drug was administered for 10 days, not for 4 or 5 days. Many other studies have shown that a most important effect of treatment of upper respiratory infections with penicillin is to prevent rheumatic fever, and this requires treatment for 10 days. This, of course, applies only to patients with group A streptococcal infections.

On page 572 the authors cite the data of Kolmer and associates in support of the validity of their concept that pharyngeal smears may be used as "an index of morbidity of upper respiratory diseases," whatever that means. I have read in detail the paper by Kolmer and associates and I am unable to find such supporting data. Indeed, Kolmer and associates did not even perform smears of the pharynx as described by the authors of the present paper.

Perhaps the most important defect is the absence of controls. The figure on page 573 represents the reduction in gram-positive cocci after 24 hours of therapy. It should be pointed out that the initial and follow-up smears were not made under identical conditions; the first swabbing was often made at home, and presumably the broth was carried about for varying periods of time before being smeared or refrigerated. During this time bacterial growth may have appeared, depending on the environmental temperature. (The study was performed from April to September.) The second smear was usually made in the office, and it is likely that less time for bacterial multiplication existed. Furthermore, even if a reduction in gram-positive cocci could be demonstrated by properly controlled observations, this cannot be interpreted as indicating that these cocci were responsible for the observed illness, or even that they might be considered undesirable flora. The effects of penicillin on a bacterial population are not limited to susceptible organisms which are producing disease; other sensitive but innocent cocci may be affected. Therefore these data are meaningless to me.

. . . on page 575 the authors talk about frequently identified pathogenic bacteria, including the hemolytic streptococcus, pneumococcus, and *Streptococcus viridans*. There is no evidence that the pneumococcus or the *Streptococcus viridans* in the pharynx induce any sort of symptomatology. Indeed, the only bacterial agents responsible for pharyngitis on the basis of reasonable evidence are group A beta hemolytic streptococci and the diphtheria bacillus. Many studies have shown that the other organisms are normal pharyngeal flora.

I should also like to point out that the authors' figures do not add up. In Table II, 30 of the 81 patients are recorded as exhibiting beta hemolytic streptococci in the pharynx. In contrast to this, in Table III, it is reported that beta hemolytic streptococci were recovered from 19 per cent of cases before treatment. Thirty is not 19 per cent of 81.

On the same page the authors have described their clinical evaluation of the response of the patients to penicillin V. It should be pointed out that here, again, no controls have been employed. In the experience of most pediatricians, the majority of acute upper respiratory infections in childhood are self-limited and short-lived. It would be important to compare the group who received penicillin with a similar group of patients who received no antibiotic. Otherwise no conclusions may be drawn.

Finally, I should like to point out that no follow-up cultures were performed. In the patients with beta hemolytic streptococci it would be important to know whether the organism was eradicated by treatment and did not reappear subsequently. As is well known, rheumatic fever is not prevented if the organism is not eradicated. Since the incidence of rheumatic fever following untreated streptococcal infections is only about 3 per cent, the fact that rheumatic fever failed to appear in this small group is meaningless.

. . . the publication of papers such as this is unfortunate from the standpoint of both the medical profession and patients, because physicians who are not well acquainted with the bacteriology of upper respiratory disease may not recognize the lack of validity in this study.

EDWARD A. MORTIMER, JR., M.D.
Cleveland, Ohio

To the Editor:

One questions the judgment of . . . publishing the paper by Wheeler, Plotkin, et al., entitled "Acute Upper Respiratory Disease: Clinical and Bacteriological Response to Short-Term Treatment With Penicillin V," which appeared in the November issue of the JOURNAL. The paper . . . may be misleading. . . . It is implied that such a course of treatment could replace the generally accepted 10 day course of treatment for streptococcal infection . . . for the prevention of rheumatic fever.

. . . By demonstrating a marked reduction of gram-positive cocci in the treated series they seek to prove their point. They state further that no complicating rheumatic fever or nephritis occurred in their series.

This reasoning is based on false premises and is misleading. The staining characteristics of bacteria can be changed by changing their environment.[1] Specifically, the gram positiveness of streptococci can be altered by the presence of penicillin in the cultural environment—be this artificial media, or their natural habitat in the nasopharynx. Furthermore, penicillin is so effective in inhibiting the growth of streptococci that a culture taken 24 hours after the institution of treatment will usually show marked reduction in growth, even though the organisms are merely inhibited, and not eradicated. This is the point . . . *it must be maintained for 10 days.* Patients treated for five days with penicillin showed persistence of the infecting type of streptococcus in 12 per cent of cases.[2, 3] The frequency of rheumatic fever following untreated streptococcal infections is usually quoted as 3 per cent. If following 5-day treatment with penicillin, roughly 10 per cent of patients still harbor hemolytic streptococci, one might then expect the incidence of rheumatic fever in a group so treated to be $\frac{1}{10}$ of 3 per cent. Wheeler and Plotkin report no complicating rheumatic fever in their series, and indeed there should have been none if one accepts 3 per thousand as the expected rate following such a course of treatment. . . .

. . . publication of this paper . . . is challenged from another standpoint: . . . The 5-day duration of treatment corresponds to the volume of the contents of one bottle of V-Cillin Suspension, Lilly . . . the detail man . . . can now quote . . . in selling the product for short-term therapy. . . .

RALPH L. ZUCKER, M.D.

Toledo, Ohio

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2. Hauser, H. B., Eckhardt, G. C., Hahn, E. D., Denny, F. W., Wannamacher, L. W., and Rammelkamp, C. H.: Effect of Aureomycin Treatment of Streptococcal Sore Throat on the Streptococcal Carrier State, Pediatrics **12:** 593, 1953.
3. Hauser, H. B., and Eckhardt, G. C.: Recent Developments in the Prevention of Rheumatic Fever, Ann. Int. Med. **37:** 1035, 1952.

To the Editor:

Thank you for forwarding to me the comprehensive critique from Dr. Mortimer. . . .

The first point raised by Dr. Mortimer concerns the duration of treatment. On page 572 we admitted that our dosage and length of treatment were arbitrarily chosen; and, in the same sentence, we conceded that the generally accepted viewpoint is to continue treatment for a week to ten days. Our arbitrary choice was based on two considerations: (a) the individual dosage calculated on a weight basis was somewhat higher than generally prescribed, and (b) we anticipated that the majority of cultures from our patients would not yield hemolytic streptococci.

Another factor, one which plagues the practicing physician, is the reluctance of parents to continue an antibiotic for a full ten days when their child has seemed well two or three days after treatment was started. Therefore, our dosage and length of treatment constitute a compromise which we considered not unreasonable.

The technique of reporting the percentage of gram-positive cocci in a smear of pharyngeal secretions is one which was utilized by Strumia during World War II. . . . With limited laboratory facilities available, he used this method to screen potentially morbid patients, culturing those who showed a high percentage of gram-positive cocci. Actually, Kolmer did not do smears in the article cited; however, he did show an increase of isolation of gram-positive cocci from throats of patients with the common

cold. Especially, he showed an increase of recovery of beta streptococcus and pneumococcus. In addition, Wilson and Miles[1] . . . tables on the bacterial flora in the nasopharynx of the general normal population show that gram-negative forms strongly prevail.

The next point raised by Dr. Mortimer seems to be divided into two parts: (1) the lack of controls, and (2) the technique of collecting samples for smear studies.

1. In the planning of this study, we discussed numerous ways to establish controls, and our conclusion was that it was impractical. The only random method would have been to give nonantibiotic treatment to alternate patients. Assuming that we could obtain full parental cooperation on this (and this is a large assumption in a private practice), we would then have the problem of matching patients, such as comparing a child of 9 in an apartment house with a toddler of 1½ in a relatively isolated rural area. We felt that it would not be feasible to try to match such varied environmental conditions as age, school contacts, degree of population congestion, etc. For this reason we decided to let the patients be their controls; i.e., if the changes we noted be random, this would indicate no effect of treatment; if the changes be statistically significant, then the conclusion would be that the drug did exert an effect.

2. We offer no defense concerning the technique of taking smears. This technique is fully described in the text of the paper, and readers may draw their own conclusions.

As to whether the pneumococcus or a combination of the pneumococcus and *Streptococcus viridans* can produce a pharyngitis, Kolmer, in the article cited, showed that bacterial complications of the pharynx during a common cold was to be considered an entity. Also, *Streptococcus viridans* was definitely shown to be pathogenic.[2]

Table III shows that hemolytic streptococci were recovered from 19 per cent of 162 cultures, not cases, as Dr. Mortimer misinterpreted. Inasmuch as the patients served as their own controls, we prepared this table to show the percentages of the total numbers of cultures taken. The figure of 30 instances of isolation of hemolytic streptococci actually becomes 30/162, or 18.55 per cent, which we rounded out to 19 per cent.

It would, indeed, be important to have controls. However, the scope and plan of this work did not lend itself to such a large study. We hope to plan such a work soon. We have already begun a follow-up study to determine the bacterial flora in patients 10 to 14 days after they have been treated with penicillin V.

Finally, we agree that this paper may be unscientific. It is difficult to conceive a clinical study where subjective data are entirely eliminated. We attempted to keep such subjective data at a minimum. As to the article being inconsistent, we cannot agree. We attempted to show that patients could and would take penicillin V. We showed that the condition of most patients who took penicillin V for upper respiratory disease improved. We reported no serious reaction. These points we set out to demonstrate, and we feel that we did, indeed, demonstrate them. The paper is not inaccurate. All data are reported as found.

JAMES E. WHEELER, M.D.

Newtown Square, Pa.

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News and Notes

The **Raymond Blank Memorial Hospital for Children** will hold its annual Pediatric Conference on February 27 and 28, 1959. Among those taking part are Dr. Waldo Nelson of Philadelphia, Dr. Joseph Boggs of Chicago, Dr. Samuel Spector of Cleveland, Dr. Harry Medovy of Winnipeg, Canada, and Dr. Wallace McCrory and Dr. Charles Read of Iowa City. Doctor Nelson will deliver the Lee Forest Hill lecture and will speak on "Infections in the Newborn Infant." For further details, write Raymond Blank Memorial Hospital for Children, Des Moines 9, Iowa.

The American College of Allergists Graduate Instructional Course and Annual Congress will be held March 15 to 20, 1959, Mark Hopkins Hotel, San Francisco, Calif. For information, write John D. Gillaspie, M.D., 2049 Broadway, Boulder, Colo.

There will be a Fellowship available in the **Children's Epilepsy Clinic of the Harriet Lane Home, Johns Hopkins Hospital,** beginning July 1, 1959. The salary for the Fellowship is $3,000.00 per annum. In addition to receiving training in pediatric epilepsy and electroencephalography, there is opportunity to attend conferences in all other phases of pediatrics. Detailed information may be obtained from Dr. Samuel Livingston, Harriet Lane Home, Johns Hopkins Hospital, Baltimore 5, Md.

Between the dates of Feb. 16 and 21, 1959, a five-day intensive course in pediatric dermatology will be offered by the **Department of Pediatrics and the Division of Dermatology of Tulane University School of Medicine,** New Orleans. It will cover infections of the skin, superficial and deep mycoses, congenital and acquired tumors, systemic and metabolic disorders, and allergic problems. Guest speaker will be Dr. Arthur C. Curtis, Professor of Dermatology, University of Michigan Medical School, Ann Arbor. There will be didactic lectures and demonstration of clinical material. Students will have an opportunity to learn at first hand techniques applicable to diagnosis of skin diseases in childhood.

Books

Recent Advances in Paediatrics. Edited by Douglas Gairdner, M.A.(Cantab.), D.M.(Oxon.), F.R.C.P., Boston, 1958, Little, Brown & Co., 378 pages. Price $9.50.

A volume of excellent reviews on selected pediatric subjects of current interest, which is not to be confused with *Advances in Pediatrics* edited by Dr. S. Z. Levine. Dr. Gairdner, of Cambridge, contributes a chapter on "The Hematology of Infancy." The other twelve reviews in the volume are two on "Jaundice in the Newborn, Non-obstructive and Obstructive," by Lathe, Claireaux, and Norman; "Physical Growth," by Falkner, now at Louisville; "The Nephrotic Syndrome," by McCrory of Iowa and Fleisher of Philadelphia; "Rheumatic Fever," by Illingworth of Sheffield; "Hypothyroidism," by Hutchison of Glasgow; "Tuberculosis," by Miller of Glasgow; and four by surgeons. These last are discussions of "Spina Bifida Cystica and Hydrocephalus," by G. H. Macnab, Surgeon to the Great Ormond Street Hospital; "Pyogenic Osteitis," by Bremner and Neligan of Newcastle; and

"The Deaf Child," by Edith Whetnall of the Auditory Unit of the Royal National Throat, Nose and Ear Hospital, London.

The last *Advances in Paediatrics* was published in 1954, and Dr. Gairdner in his foreword to this volume comments that it seems likely that pediatrics has entered an era where pediatric research must turn increasingly to the fundamental biological sciences upon which pediatrics itself depends, a viewpoint that was so strongly brought out in the study by the American Foundation, "Medical Research" (J. PEDIAT. 48: 691, 1951) as true for all branches of medicine. We would rank this volume high among the similar collections of pediatric reviews that are appearing. The reviewer's chief criticism is that apparently in an attempt to keep the size of the volume down, the publishers (Churchill, of London) have used a rather small and closely set font of type which is tiring to the reader, particularly as most readers will turn to the reviews after a day of hard work.

B. S. V.

Modern Trends in Pediatrics, Second Series. A. Holzel and J. P. M. Tizard, New York, 1958, Paul B. Hoeber, Inc. Price $14.00.

The first of this series was published in 1951 and edited by the late Sir Leonard Parsons. The present authors have maintained the same high standards.

A number of new authors as well as new titles appear. There are chapters on mortality in childhood in England and Wales, experimental and human genetics, and neonatal pathology. K. W. Cross writes on anoxia in the newborn; R. B. Zachary on neonatal surgery; J. D. L. Reinhold on heart disease; and Wolf Zuelzer on pediatric hematology. There are chapters on virus diseases in childhood, malignant disease, allergy, convulsions in childhood, neurosurgery, and child psychiatry. A. M. Bongiovanni and W. R. Eberlein wrote the chapter on corticosteroids in therapy; T. Stapleton the chapter on metabolism; and J. H. P. Jonxis on chromatography and electrophoresis. "The Work of a Pediatrician in a Provincial Town of the Union of Socialist Soviet Republics" is a timely and interesting chapter. No attempt is made to survey the entire subject of pediatrics. However, the volume will prove very valuable for its authoritative review of recent progress. On the whole, it is enjoyable reading. The material is well organized and the bibliographies following each chapter are excellent.

The book is recommended as a source of authoritative, up to date, factual information which is presented concisely.

B. M. K.

Tumors of the Liver and Intrahepatic Bile Ducts. Hugh A. Edmondson, M.D., Washington, D. C., 1958, Armed Forces Institute of Pathology, 216 pages. Price $2.25.

This is Fascicle 25, Section VII of the *Atlas of Tumor Pathology*, published by the Armed Forces Institute of Pathology. Although written primarily for the general pathologist, a significant part of the fascicle is concerned with neoplasms and neoplastic-like lesions occurring in the liver of infants and children. For example, there are sections devoted to carcinoma of the liver in infancy and childhood, to infantile hemangioendothelioma, to sarcomas of the liver in infants and children, to hepatic mixed tumors, teratomas, and to mesenchymal hamartomas. A brief summary of the embryology of the liver is included and the clinical manifestations associated with the various hepatic tumors are described briefly. The photographs and photomicrographs are superb and constitute a considerable part of the book, but the text as well as the references make this fascicle one which should be of value to anyone interested in neoplasms and neoplastic-like lesions of the liver in early life.

J. B. A.

Editor's Column

POSTGRADUATE MEDICAL EDUCATION

MAN'S task is never done—a fact best exemplified in the construction of himself.

In recent years "continued education" or postgraduate training has become a matter of major concern in medical circles—and rightly so. This is not a new concept or situation; only the emphasis is more evident. Traditionally, the physician has "practiced medicine."

On the basis of the accepted assumption that education is self-attained and that man learns rather than is taught, a bit of self-analysis is always in order.

There are a number of reasons for the increased emphasis on formalized plans for postgraduate medical education. These include: (1) the physician's natural curiosity and a desire for self-betterment—one hopes this is the most common driving force; (2) the layman's increasingly critical appraisal of medical care—not yet the force which it should or can be; (3) the competition among physicians for standing within their community, especially among their colleagues, and for rank on hospital staffs; (4) certification by the American Academy of General Practice or by one of the medical specialty boards; and (5) in our present tax structure, the reality that the government bears a substantial part of the cost. The fact that a few physicians take undue advantage of this legal device for a "vacation" should not be construed that it is not a justified business expense for the average physician.

The editor has spent a substantial part of his professional career in an institution which had its origin in a conference setting with a tutorial form of training for a few determined students and whose early growth was supported financially by Conwell's Acres of Diamonds (strengths exist in the individual and in his local environment). Perhaps for this reason he is constrained to suggest that the individual to be truly strong must plan and guide his own postgraduate educational program.

State and national meetings and formal postgraduate conferences have important roles, but at best they are adjuncts and are accessory to the individual's basic program. This begins and is continued at home—in the physician's study, in his office, with members of his group (for those in group practice) or within a community group, in his local hospital's staff meetings and in his participation with the teaching program of his hospital or of a medical school. To the extent that the physician finds adequate growth stimuli within himself

and his immediate environment can one be confident of his growth potential.

The immediate environment obviously varies in different locales, but it also varies with different individuals within the same community.

Each of us knows physicians who have "kept up" and at 50, 70, and even beyond are in tune with the current status. Unfortunately the other end of the distribution curve is much more heavily weighted with physicians who practice essentially at the level of their attainment at the completion of their formal medical training. An evidence of what can be accomplished by determined and inspired persons is the development of sound postintern training programs in cities without a medical school. In the pediatric field, the unit in Des Moines is an outstanding example of such accomplishment.

Taking advantage of available opportunities is highly relative and a significant variable among practicing physicians. If data were available for regularly scheduled weekly conferences in hospitals of medical schools which are open to all physicians irrespective of staff appointments, it might well be found that in many of them the proportionate number of out-of-town physicians in attendance is consistently greater than that of local physicians. In some instances it would appear that the mere availability of opportunities makes them seem commonplace.

Participation in teaching and in training programs may well be the strongest and most effective stimulus for continued personal developments. The need for inclusion of practitioners in teaching programs is not lessening but rather increasing in spite of the rapid increase in the number of full-time clinical teaching personnel in our medical schools. Medical educators are aware of the importance of including the practitioner in the active faculty. It would seem a safe prediction that we will witness within the near future a much more effective organization of regional hospitals around each of our medical schools not only for postmedical school training but for undergraduate teaching as well. At the present time it is likely that most medical schools have effective clinical teachers who drive distances of a hundred miles or so each week to participate for a half day or more in clinical activities with students. It is the tested rule—he gains most who gives most.

A word may also be in order concerning short postgraduate courses. The demand for such experience is now far in excess of that which can be supplied by the national meetings of most of the medical societies. This is certainly the situation in pediatrics. The recent move of the Academy of Pediatrics to make its services available for the promotion of such courses is evidence of the increasing demand for them. It is not the intent of the Academy, however, that all postgraduate pediatric seminars should be under its supervision, nor should they be. There is a real need for continuation of locally planned and administered postgraduate courses. On the one hand, there are a large number of physicians whose practice is solely or almost wholly in pediatrics who are not members of the Academy. These physicians are in need of such educational programs and they should have ready access to them. From the

standpoint of the local unit which organizes and conducts such courses there is much to be said for the stimulus and growth potential which accrues from such activities. Those who have participated in seminars organized and conducted by a department of pediatries are aware of the favorable effects upon the department as a whole as well as upon its individual members. But irrespective of sponsorship the important factor in the conduct of such seminars or postgraduate courses is the extent to which the attending physician in his capacity as a student has the opportunity to participate. Certainly the man who comes to the seminar wants to know about recent developments and should expect that new material will be adequately presented, but he must also participate actively in discussion and contribute from his own experience if he is to secure maximum benefits from his attendance.

Irrespective of the advantages of group practice and the probability that increasing numbers of physicians will have some type of working alliance with other physicians, the very nature of medical practice speaks for and requires an intimate physician-patient relationship. The physician's role demands a strong character combined with an adequate working knowledge of his field of medical practice. This goal is never completely attainable—but fortunate is the patient whose physician has proved himself a constant student and designer of his own curriculum.